

The Resurgence of Sexually Transmitted Diseases

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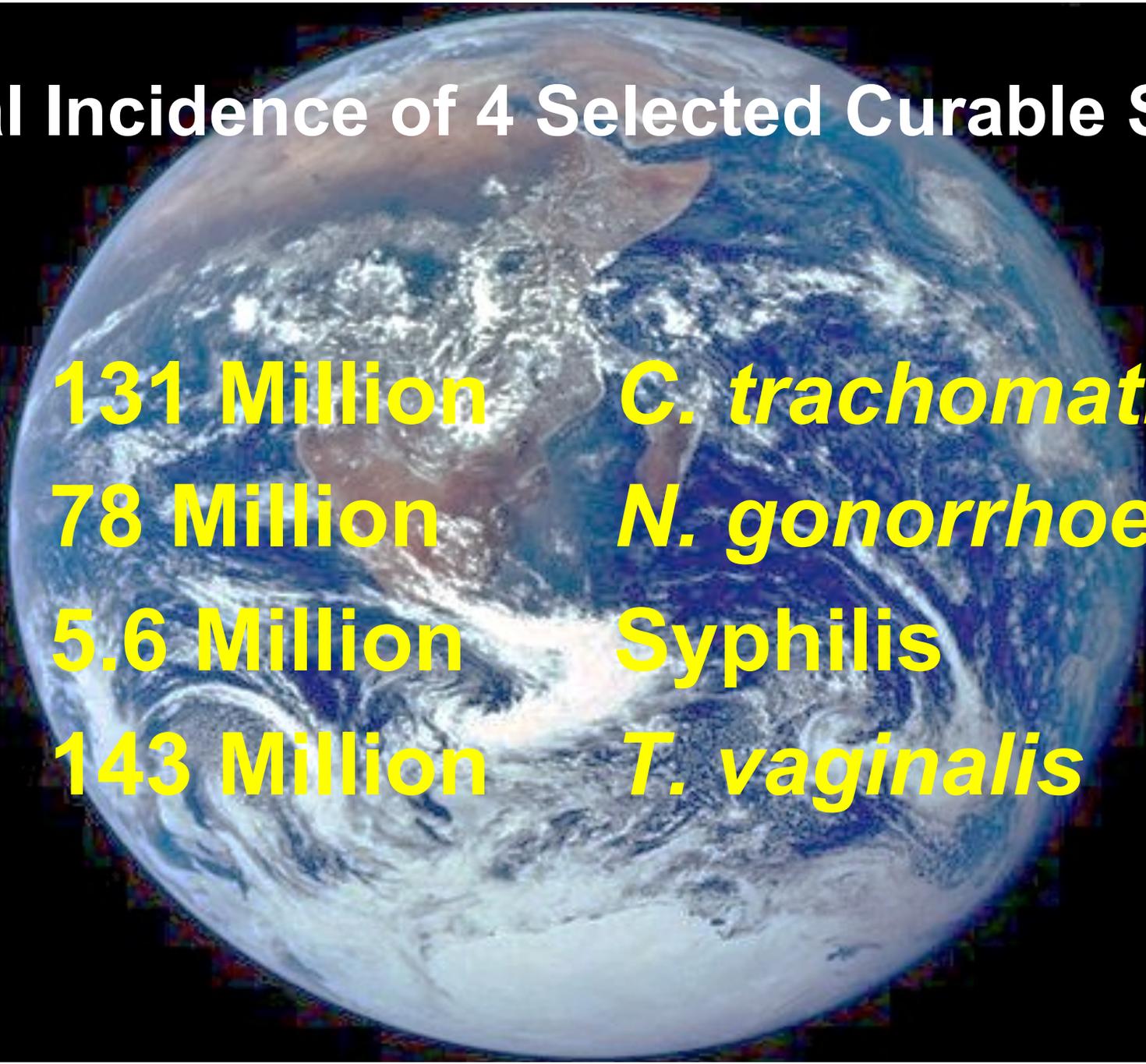
National Institute of Allergy and Infectious Diseases



Global STIs

- **> 1 Million STIs are acquired every day globally**
- **Each year, an estimated 357 million new infections occur among 4 curable STIs**
- **> 500 Million people are estimated to have genital HSV**
- **> 290 Million women have HPV infection**
- **> 900,000 pregnant women infected with syphilis resulting in 350,000 adverse birth outcomes**
- **Drug resistance, especially for gonorrhea is increasing**

Global Incidence of 4 Selected Curable STIs



131 Million

C. trachomatis

78 Million

N. gonorrhoeae

5.6 Million

Syphilis

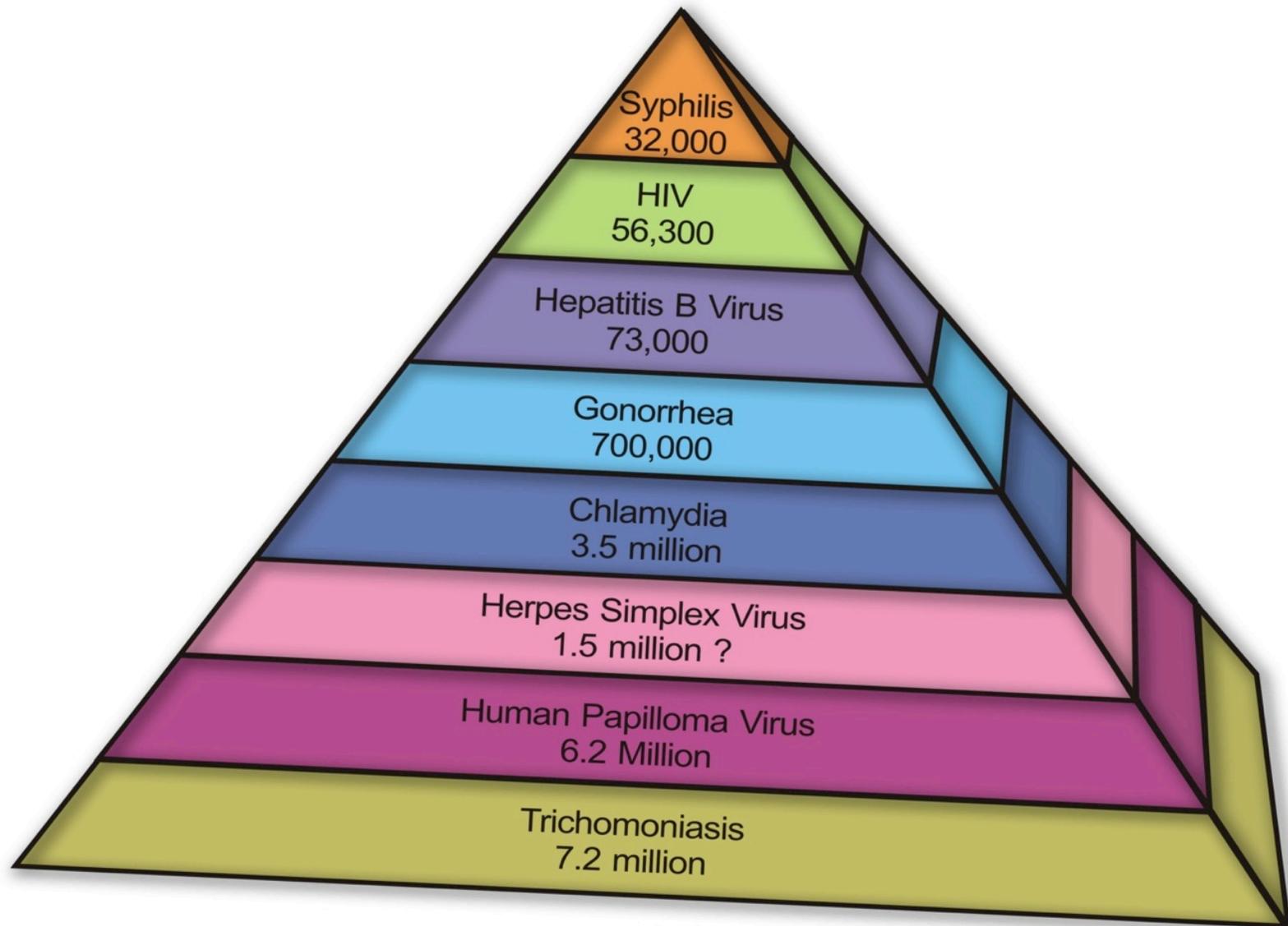
143 Million

T. vaginalis

STDs in the US

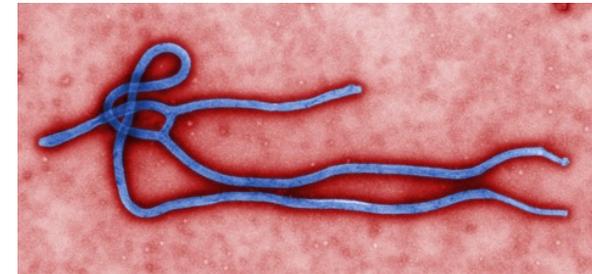
- **> 20 million new STDs in the U.S. annually**
- **>2 million cases of the three nationally reported STDs – chlamydia, gonorrhea, and syphilis – were reported in the U.S. in 2016, highest number ever.**
- **More than half of persons who contract STDs are under age 25**
- **All STDs have significant health disparity issues with rates often 10 times higher in Blacks**
- **STDs increase the risk of acquiring HIV**
- **The costs associated with these STDs are increasing:
>US \$16 Billion Annually; Funding for screening declining**

US Estimates of Sexually Transmitted Infections

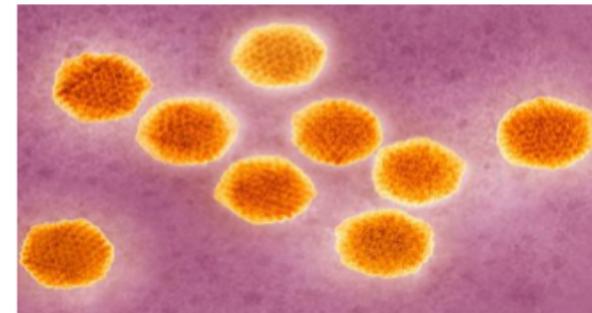


Newly Recognized STIs

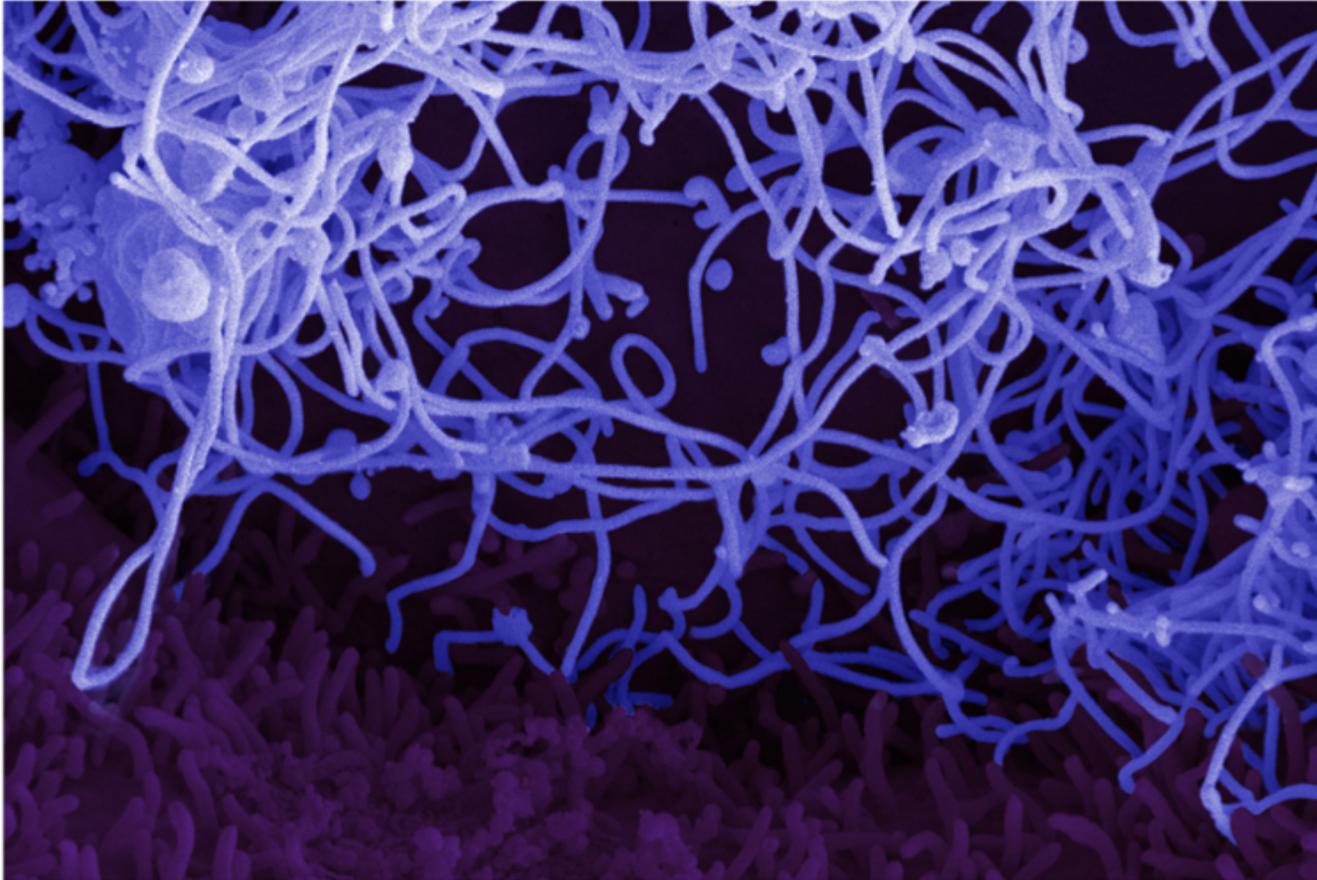
- **Ebola and Marburg Filoviruses: Virus is detectable in semen for 82 days and RNA >13 months; Immunologic privileged sites/sanctuary**



- **Zika: 17 studies documenting sexual transmission and virus detectable in semen over 180 days**



Ebola virus has lurked in a man's semen for more than 500 days

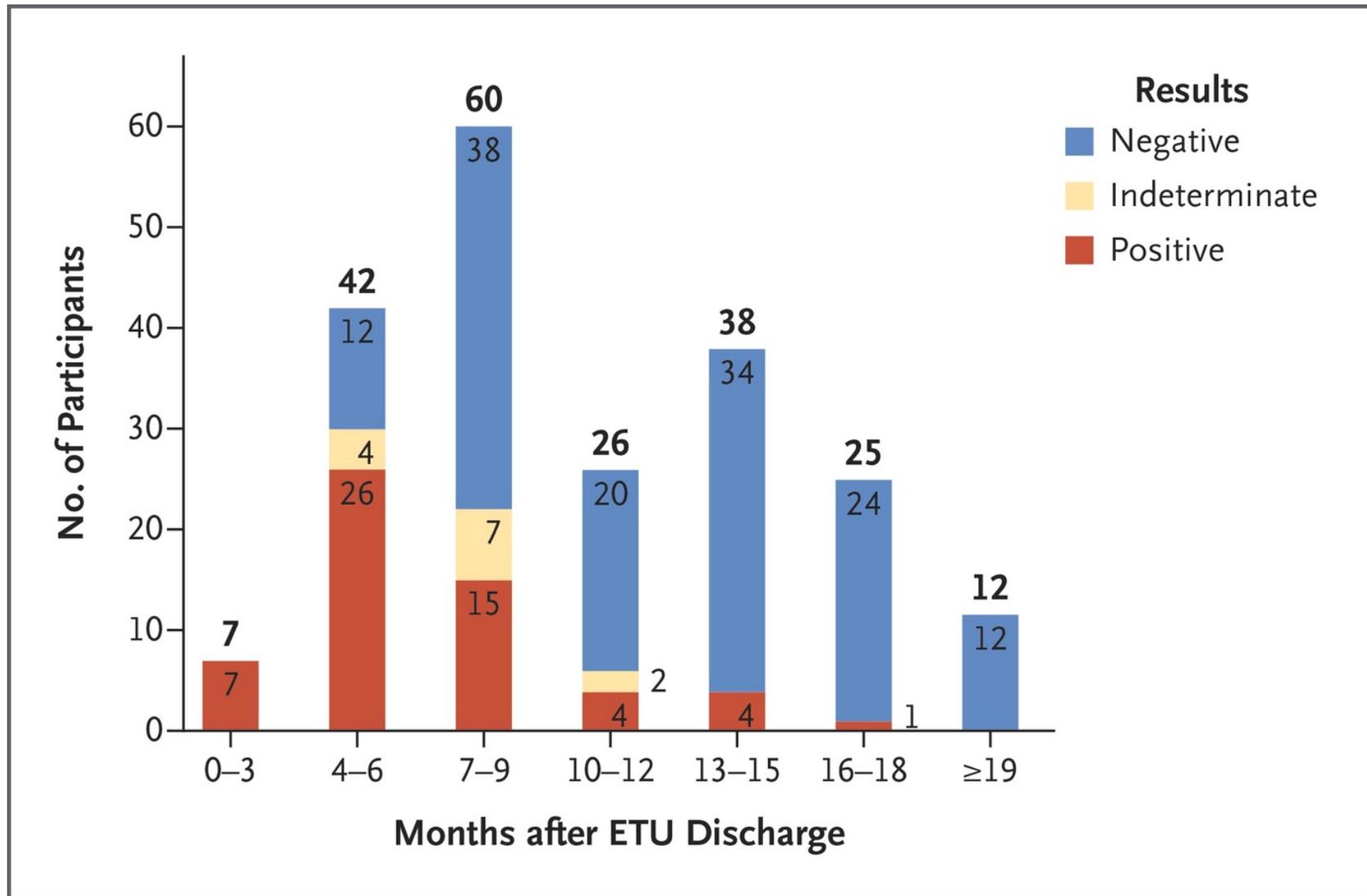


How long can it hide?
NIAID

By Debora MacKenzie

The [Ebola virus](#) can persist in a man's semen for much longer than we thought. A man in Guinea who survived Ebola in 2014 is now known to have carried it for at least 531 days. Earlier this year, he transmitted the virus sexually, causing it to spread to at least 10 people, and killing 8 of them.

Results on RT-PCR in Semen Specimens from Survivors of Ebola Virus Disease



Prevention of Sexual Transmission of Ebola

- **Men who have recovered from Ebola should abstain from sex for a minimum of three months if not longer.**
- **If abstinence is not possible then condoms should be used.**

Transmission of Zika Virus Through Sexual Contact with Travelers to Areas of Ongoing Transmission — Continental United States, 2016

- **5 confirmed sexually transmitted cases in the U.S.**
- **10 countries have reported probable sexually transmitted cases (WHO, 6/30/16)**

Recommendations: Couples Trying to Conceive

Suggested timeframes to wait before trying to get pregnant		
	Women	Men
Traveled to an area with Zika or sex with a man who has been in an area with Zika		
Symptoms	Use condoms or abstain after symptoms start: at least 8 weeks	at least 6 months
No symptoms	Use condoms or abstain: at least 8 weeks	at least 8 weeks Talk to doctor or healthcare provider
Living in area with Zika		
Symptoms	Use condoms or abstain after symptoms start: at least 8 weeks	at least 6 months
No symptoms	Talk to s doctor or healthcare provider	

<http://www.cdc.gov/zika/pregnancy/thinking-about-pregnancy.html>

Clinical syndromes: Common STIs

Urethritis/ Cervicitis

- Gonorrhea (GC)
- Chlamydia (CT)
- (*Mycoplasma genitalium*)

Proctitis

- GC, CT (also LGV proctitis), HSV, Syphilis

Pharyngitis

- GC

Conjunctivitis:

- GC, CT

Genital Ulcer Disease

- Syphilis
- Herpes
- LGV, Chancroid, Granuloma Inguinale

Vaginitis

- Trichomonas
- Bacterial Vaginosis

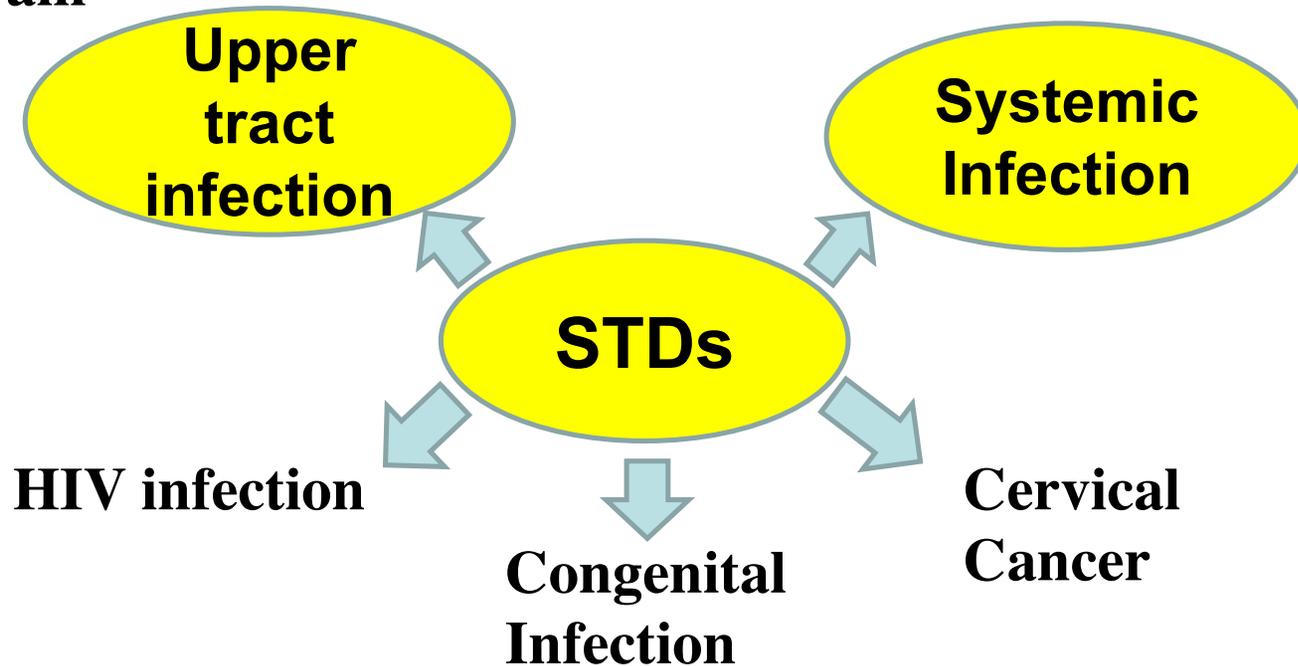
Skin lesions

- HPV-warts, cancer
- Herpes

Overview of Complications of Sexually Transmitted Diseases

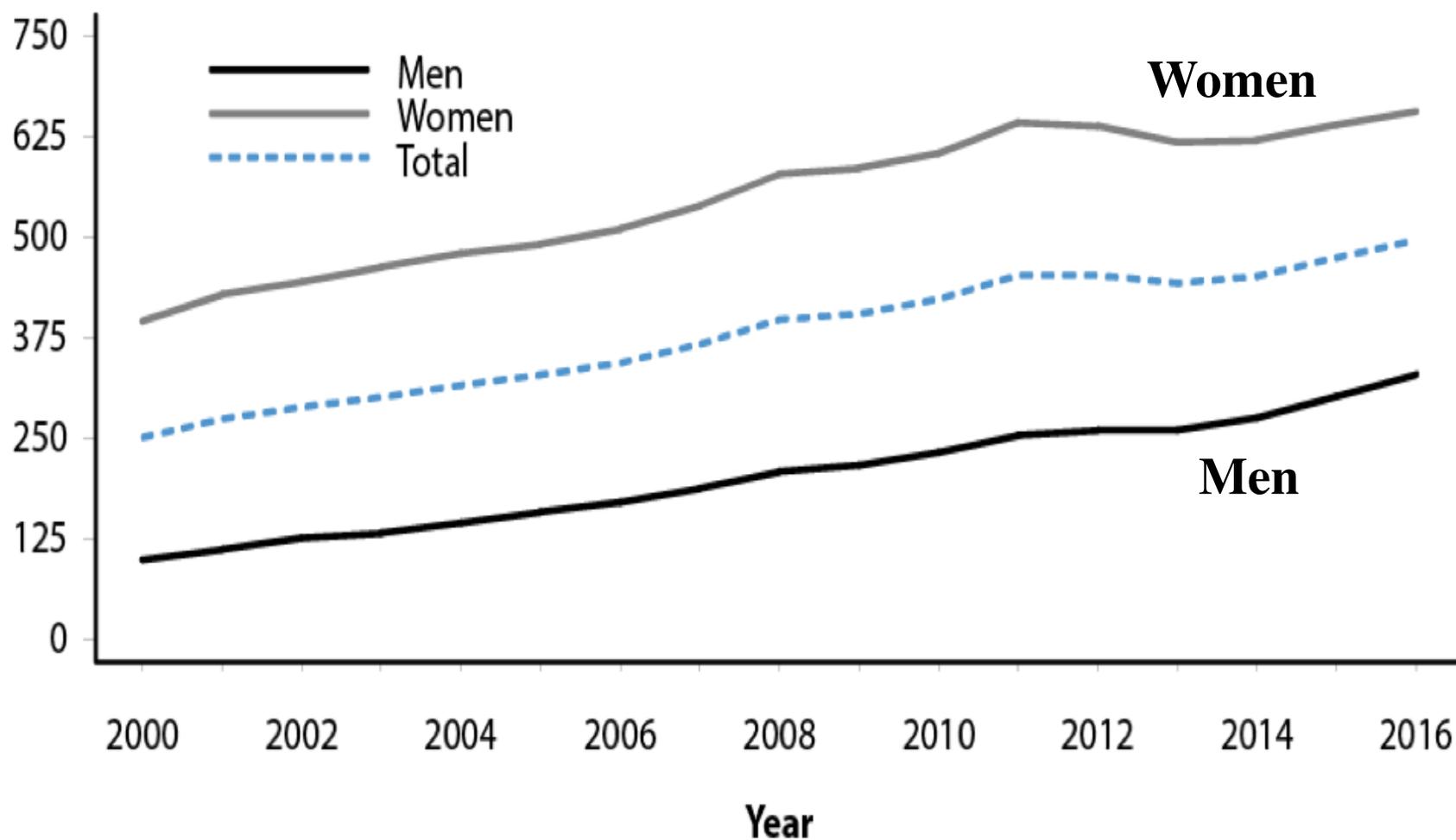
Infertility
Ectopic Pregnancy
Chronic Pelvic Pain

Fetal Wastage
Low Birth Weight



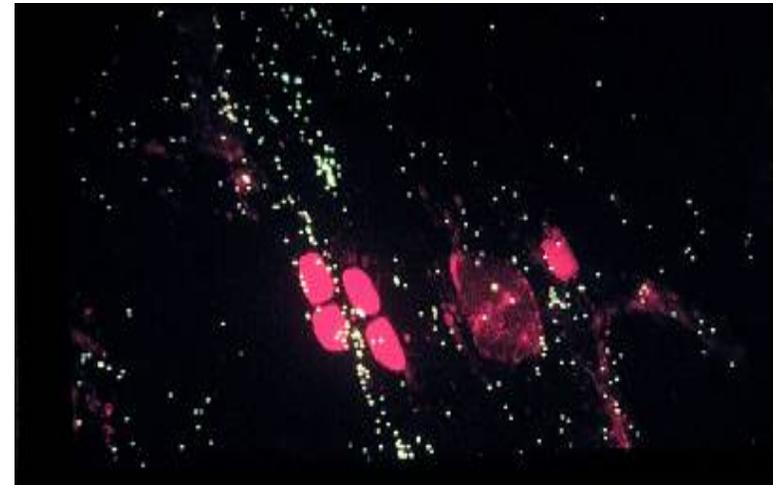
Chlamydia — Rates of Reported Cases by Sex, US, 2000–2016

Rate (per 100,000 population)

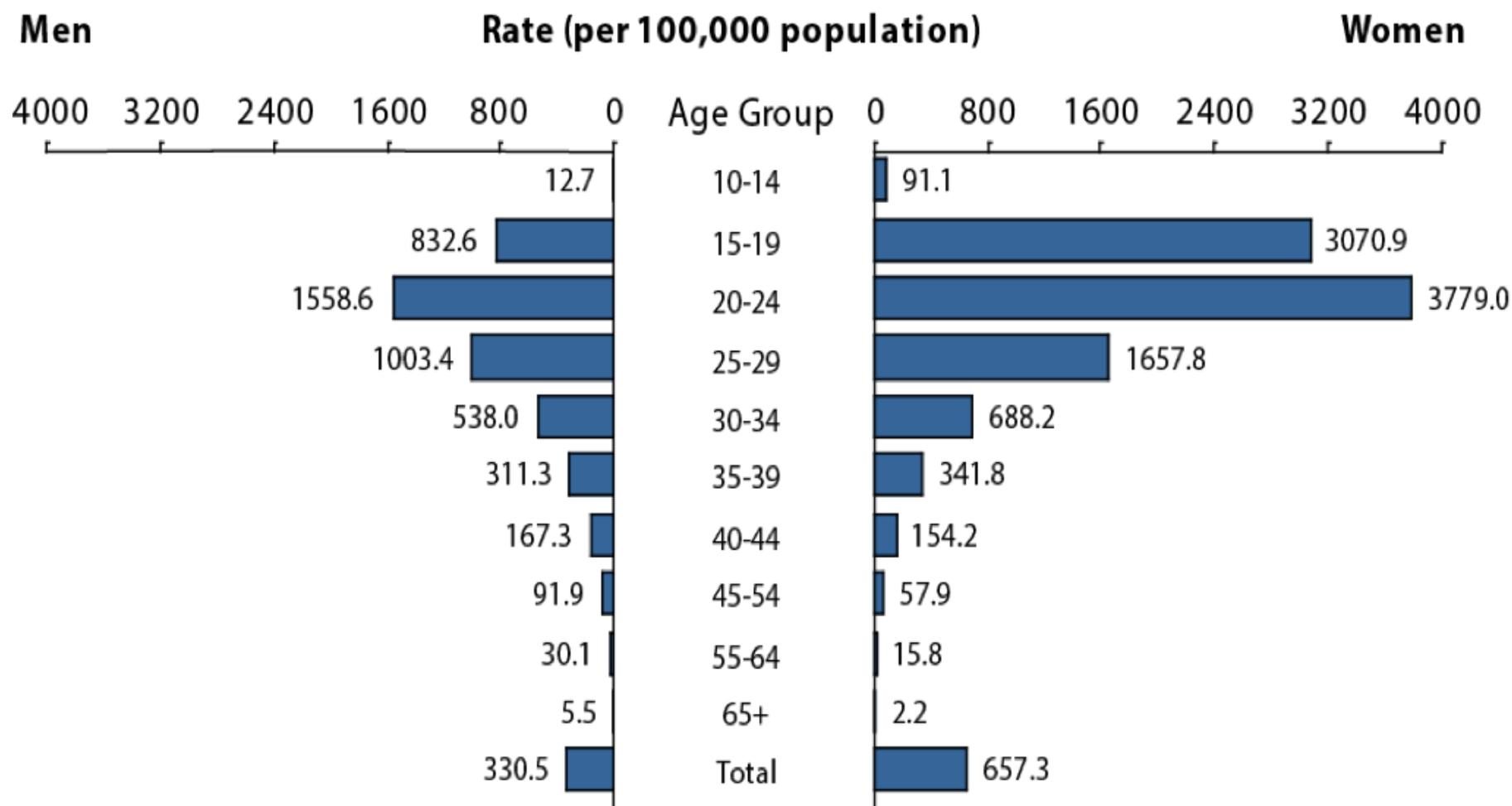


Epidemiology: *Chlamydia trachomatis*

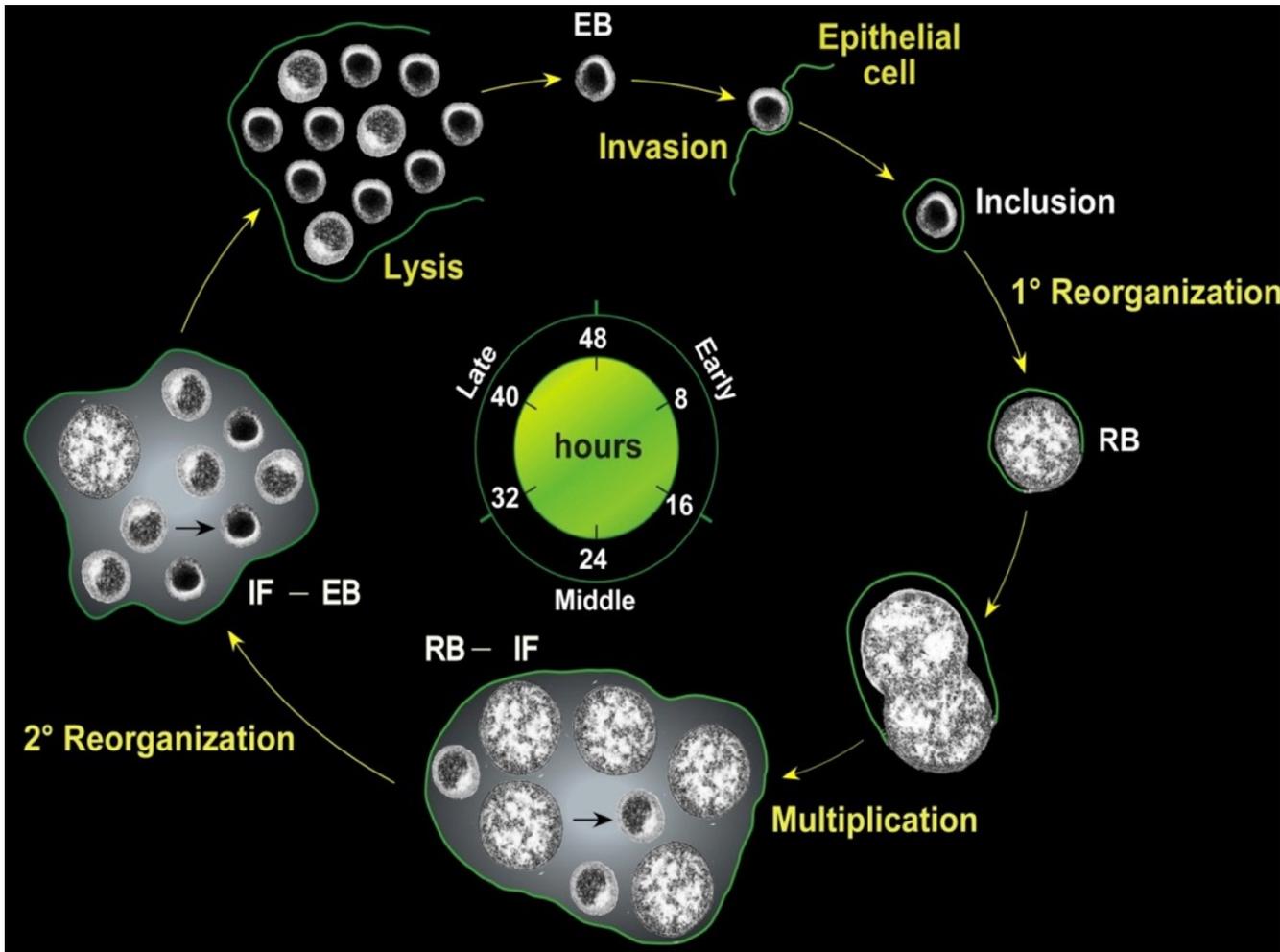
- **89 million annual new cases worldwide**
- **3.5 million new cases in U.S./year**
- **Most frequently reported STD in U.S.**
- **High prevalence co-infection in partners (>50%)**
- **Perinatal transmission can result in neonatal conjunctivitis and pneumonia in newborn infants**
- **Untreated infections increase risk for sequelae (PID, infertility, ectopic pregnancy, chronic pelvic pain)**



Chlamydia — Rates of Reported Cases by Age Group and Sex, United States, 2016

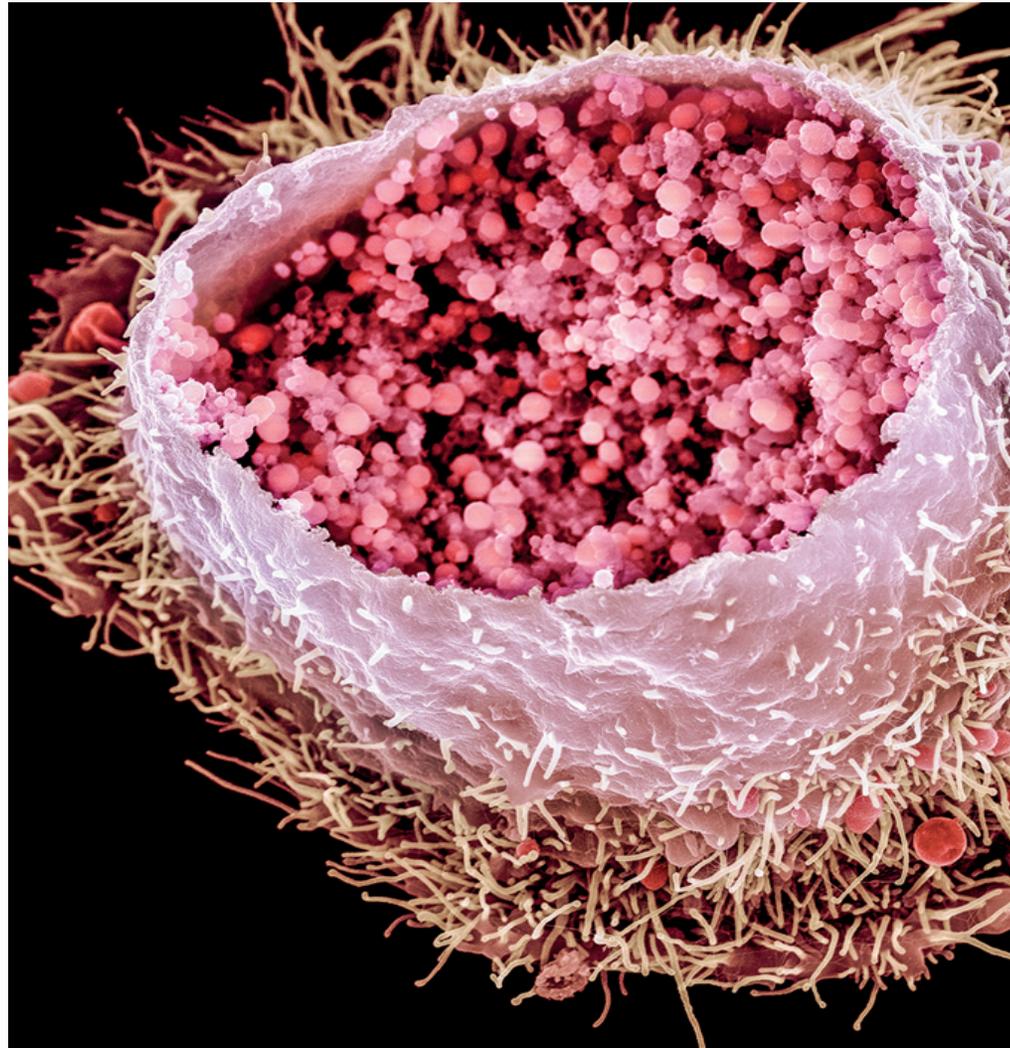


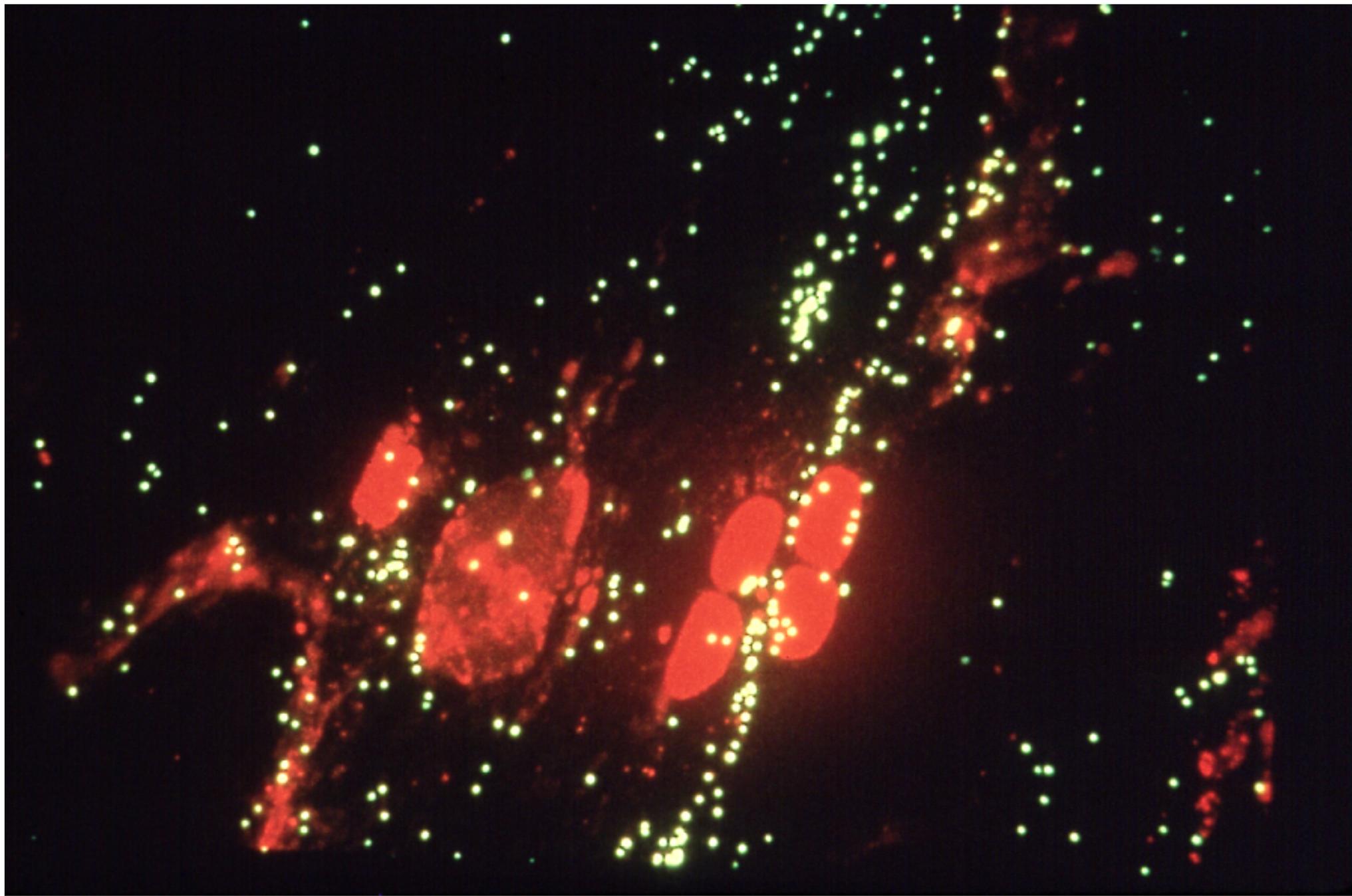
Chlamydia trachomatis



- ❖ Gram negative obligate intracellular bacteria
- ❖ Complex developmental biology modulates between infectious elementary body (EB) and non-infectious reticulate body (RB)
- ❖ Strict human pathogen
- ❖ Mucosal epithelial cell infection tropism
- ❖ Nonhuman primates only relevant infection and disease model

Chlamydia trachomatis





Chlamydia trachomatis

- **MEN**

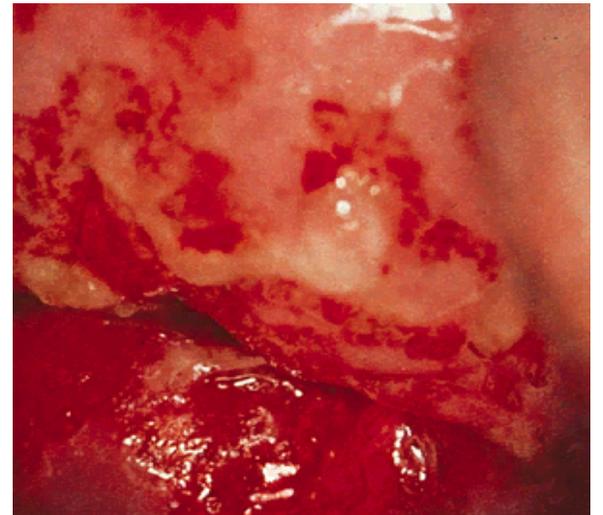
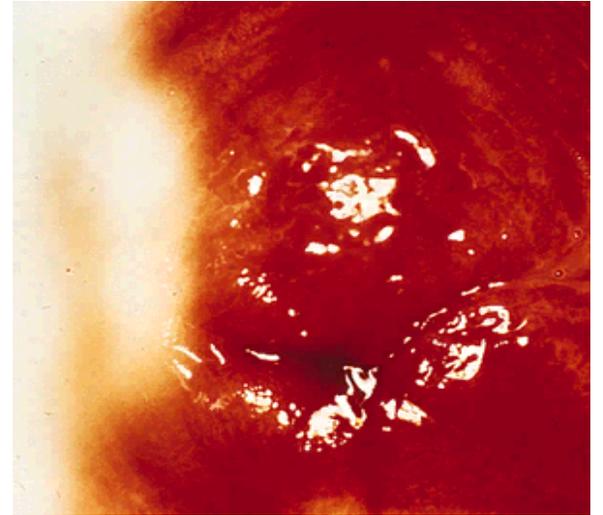
- **Asymptomatic**
- Urethritis
- Epididymitis (70% of cases in young men)
- Proctitis
- Conjunctivitis
- Pharyngitis (rare)
- Reactive arthritis (urethritis, conjunctivitis, arthritis, skin lesions)

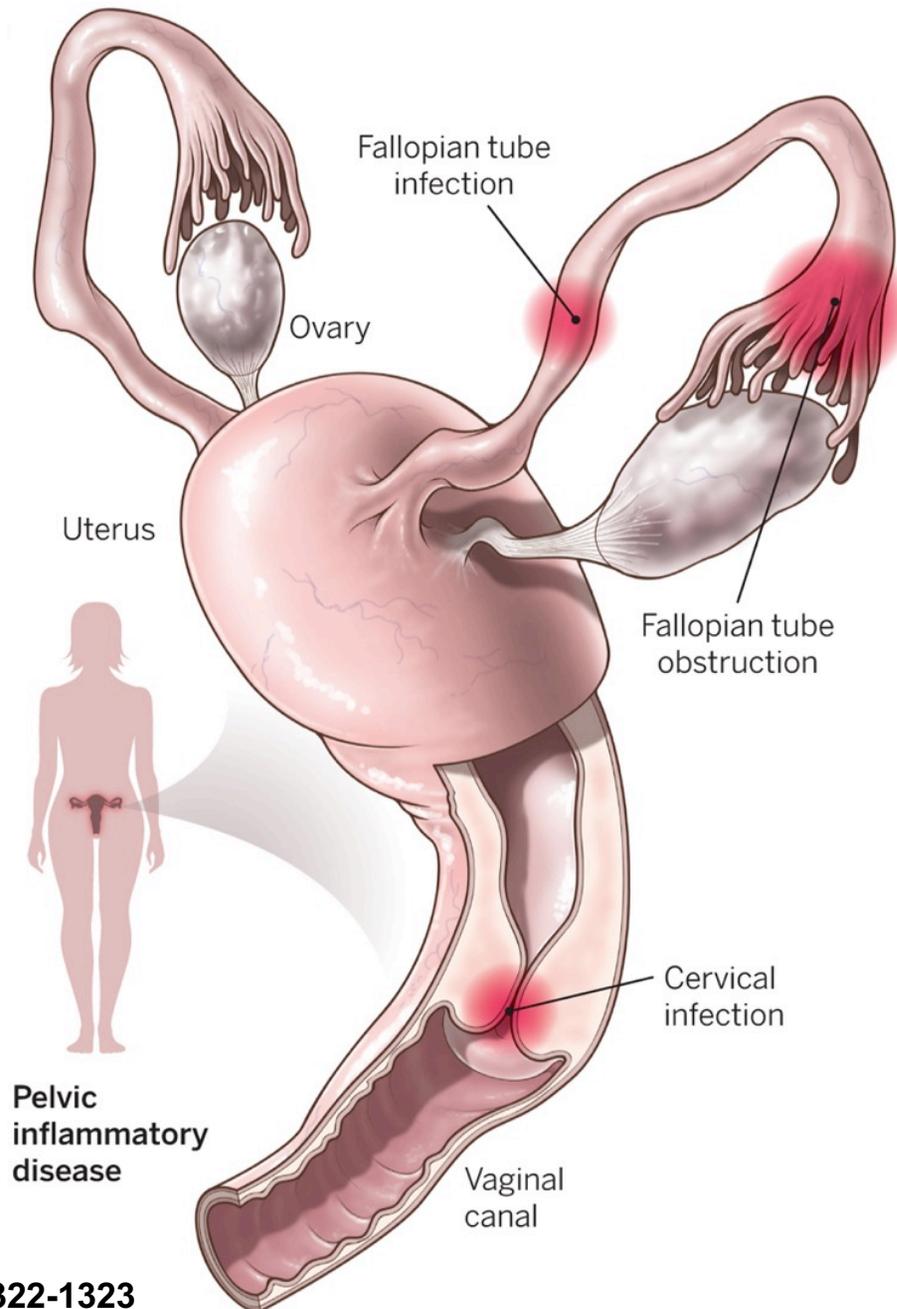
- **WOMEN**

- **Asymptomatic**
- Cervicitis
- Urethritis
- Pelvic inflammatory disease
- Bartholinitis
- Proctitis
- Conjunctivitis
- Reactive arthritis

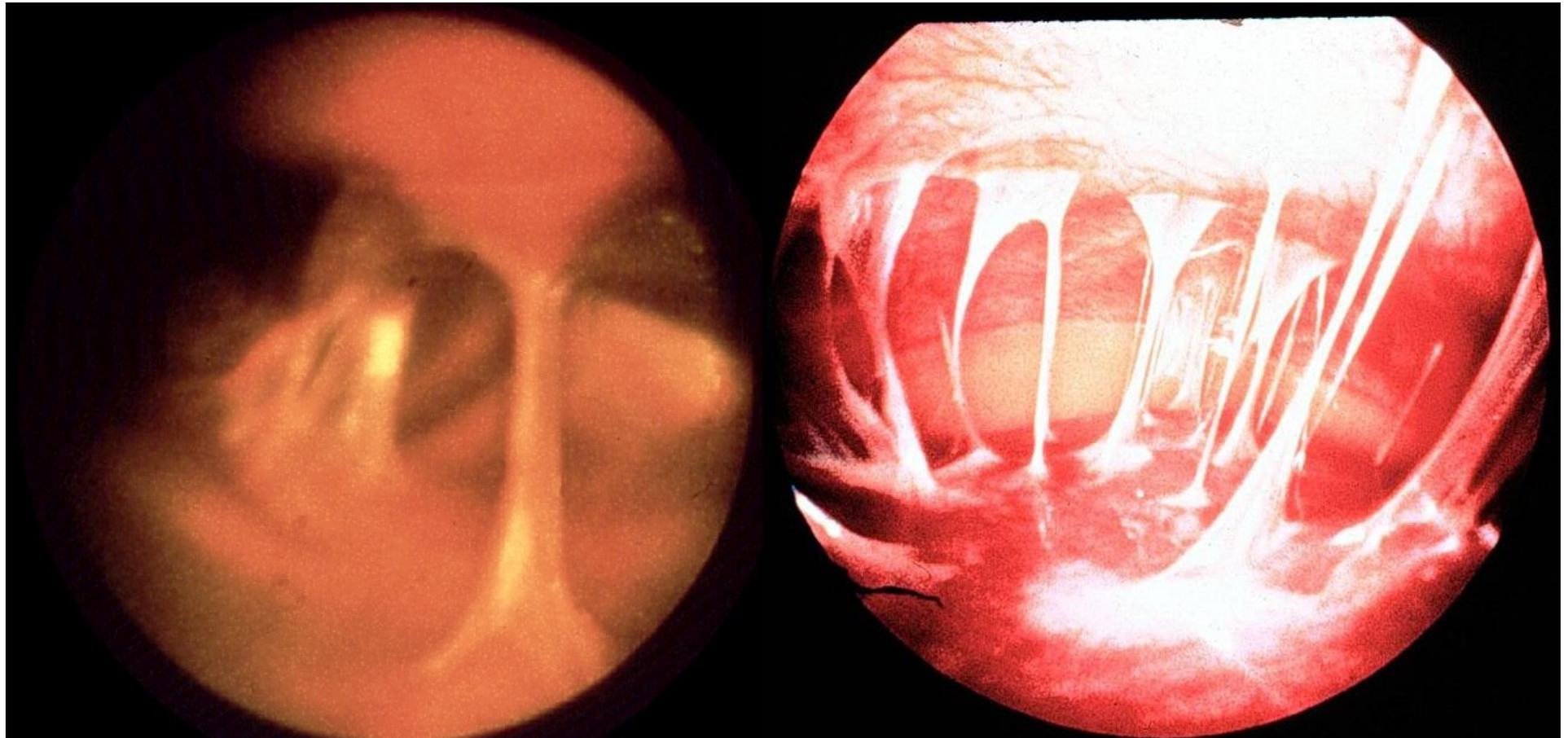
Clinical Manifestations: Women

- Majority- no signs or symptoms
- Cervicitis
 - Discharge, ectopy, edema, induced bleeding
 - 30-50% have mucopurulent cervicitis (>30 PMNs per oil immersion field)
- Pelvic Inflammatory Disease (PID)
- Ectopic Pregnancy
- Infertility





Chlamydia Adhesions: Fitz-Hugh Syndrome



Pelvic Inflammatory Disease (PID)

- **Diagnostic criteria- only ONE of the following:**
 - Cervical motion tenderness
 - Uterine tenderness
 - Adnexal tenderness
- **Hospitalize**
 - Pregnant
 - Tubo-ovarian abscess
 - Appendicitis cannot be excluded
 - Did not respond to PO antibiotics
 - Patient has nausea and vomiting, or high fevers/severe illness
 - Unreliable follow-up if treated as outpatient

Pelvic Inflammatory Disease (PID)

- Inflammation of upper genital tract
- May include endometritis, salpingitis, tubo-ovarian abscess and pelvic peritonitis
- STDs involved: GC, CT, *Gardnerella.vaginalis*, *Mycoplasma hominis*, *Ureaplasma urealyticum*; anaerobes, enteric Gram-negative rods
- Most common cause of gynecologic visits to US emergency departments
- Adolescents and young adults at high risk

Lymphogranuloma venereum (LGV)

- ***Chlamydia trachomatis* serovars L1-L3**
- **Unilateral painful inguinal lymphadenopathy; “groove sign”; initial ulcer is short-lived**
- **Rectal exposure leads to proctocolitis**
- **Dx: culture, immunofluorescence, or nucleic acid detection**
- **Rx: Doxycycline 100mg po BID X 21d**



Who to Test for Chlamydia?

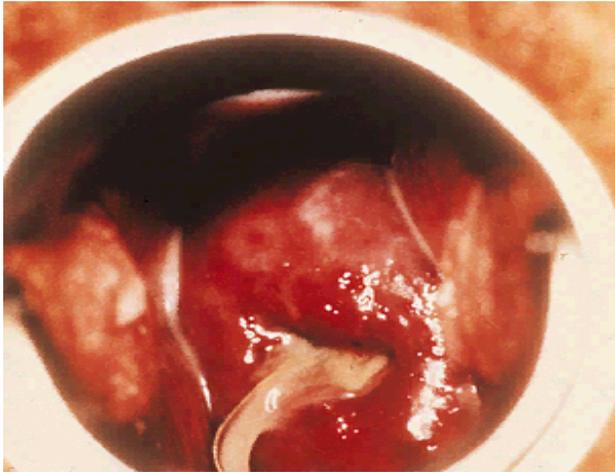
U.S. Preventive Services Task Force Guidelines

- **Women with mucopurulent cervicitis or PID (diagnostic testing)**
- **All sexually active women \leq 24 years old**
- **Annual testing for CT of all women ‘at risk’, defined very liberally (prior CT or any other STI; inconsistent condom use; new or multiple partners; exchange sex for money or drugs)**

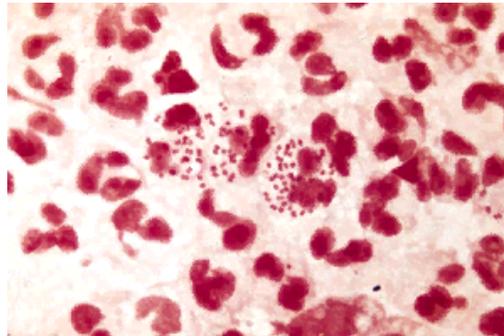
Chlamydia trachomatis treatment

- Duration of therapy depends on serotype:
 - Azithromycin 1g PO X 1d **OR**
 - Doxycycline 100mg po BID X 7d
 - L1-L3 serotypes: Doxycycline 100 mg PO BID X 3 weeks OR Azithromycin 1g PO q week X 3 weeks
- *Test-of-cure* (repeat testing 3–4 weeks after completing therapy) is not routinely recommended
- Providers also are strongly encouraged to retest all women treated for chlamydia infection whenever they next seek medical care within the following 3–12 months (**Reinfection** rates are high!)

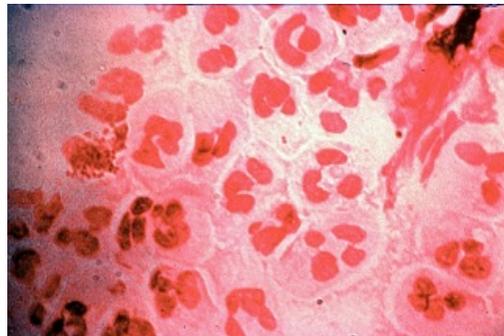
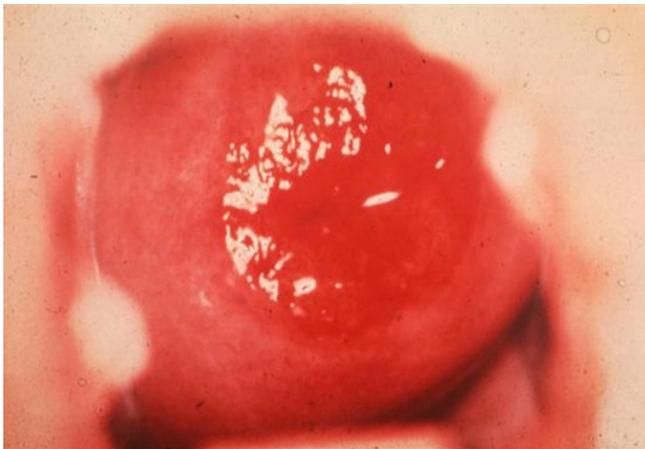
Gonorrhea vs Chlamydia: Clinical Presentation



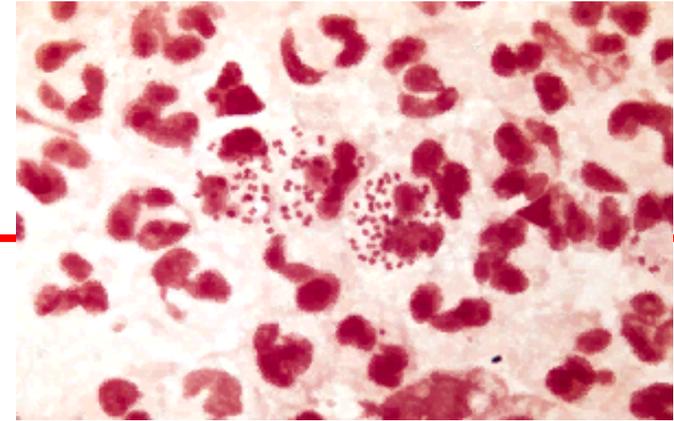
Gonorrhea



Chlamydia



Neisseria gonorrhoeae

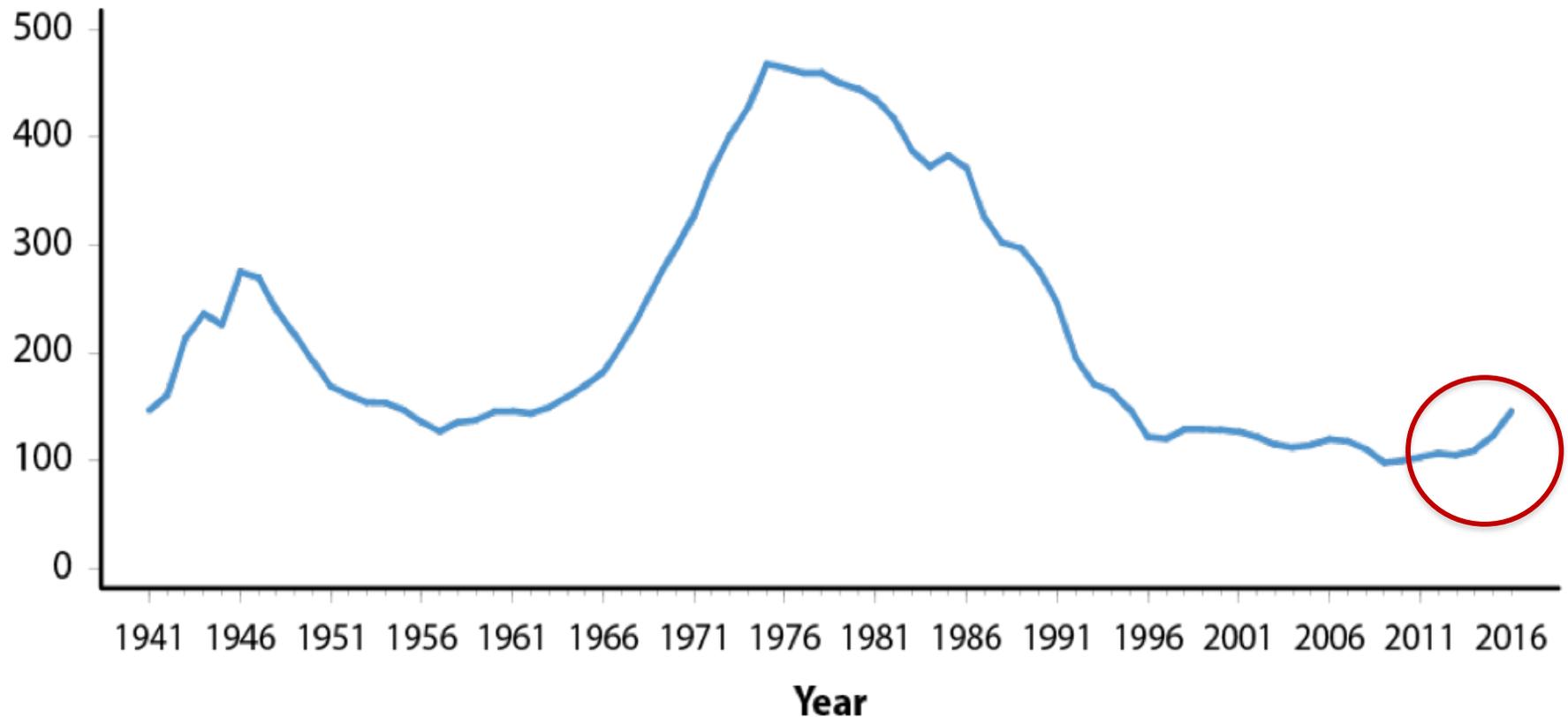


- *Gonorrhea*

- Case rate is highest of any industrialized country; 50x that of Sweden; 8x Canada.
- After declining steadily to 1996, rates level for 15 years, but now increasing last 3 years.
- For last decade cases have doubled in MSM
- **Antibiotic resistance increasing**

Gonorrhea — Rates of Reported Cases by Year, US, 1941–2016

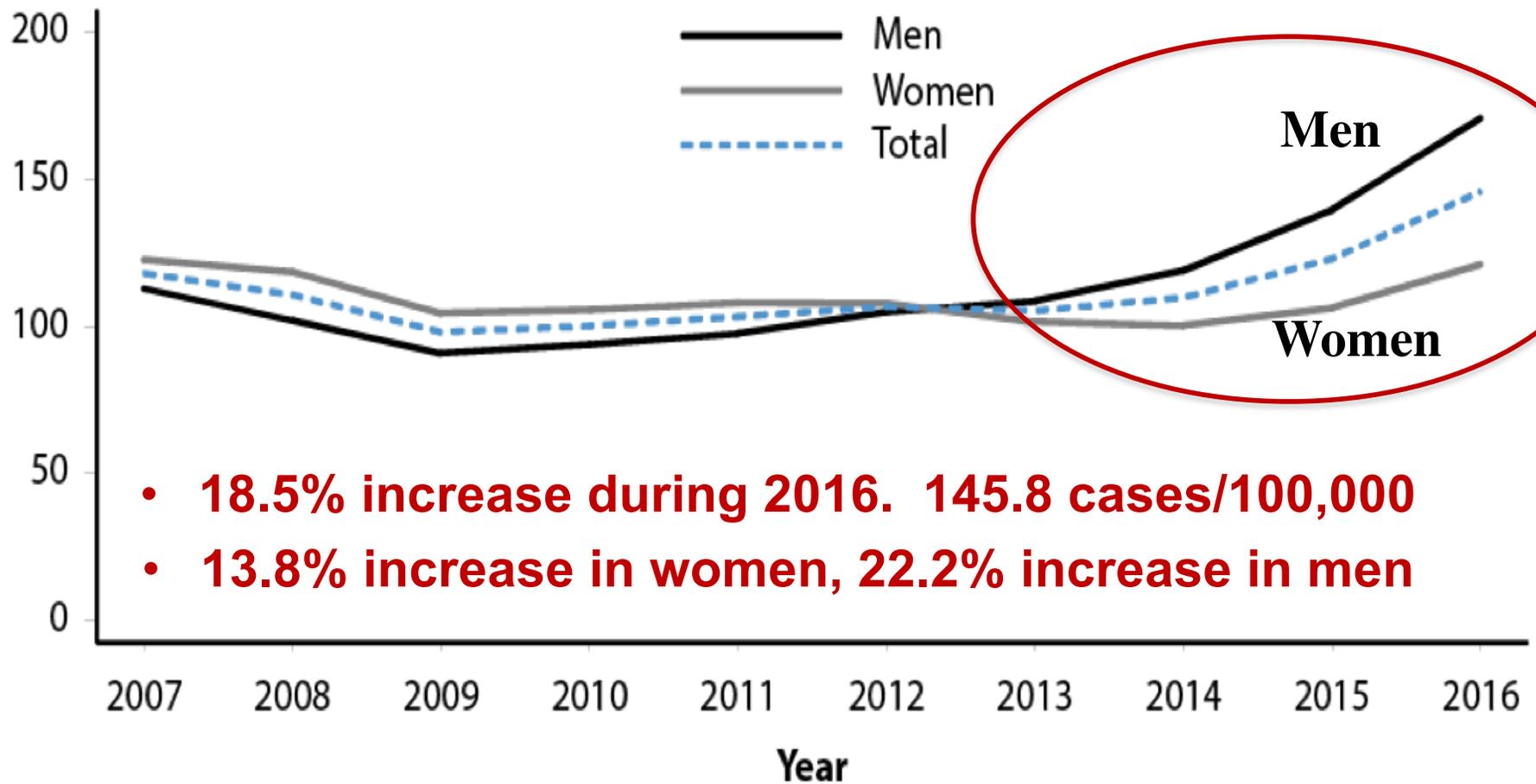
Rate (per 100,000 population)



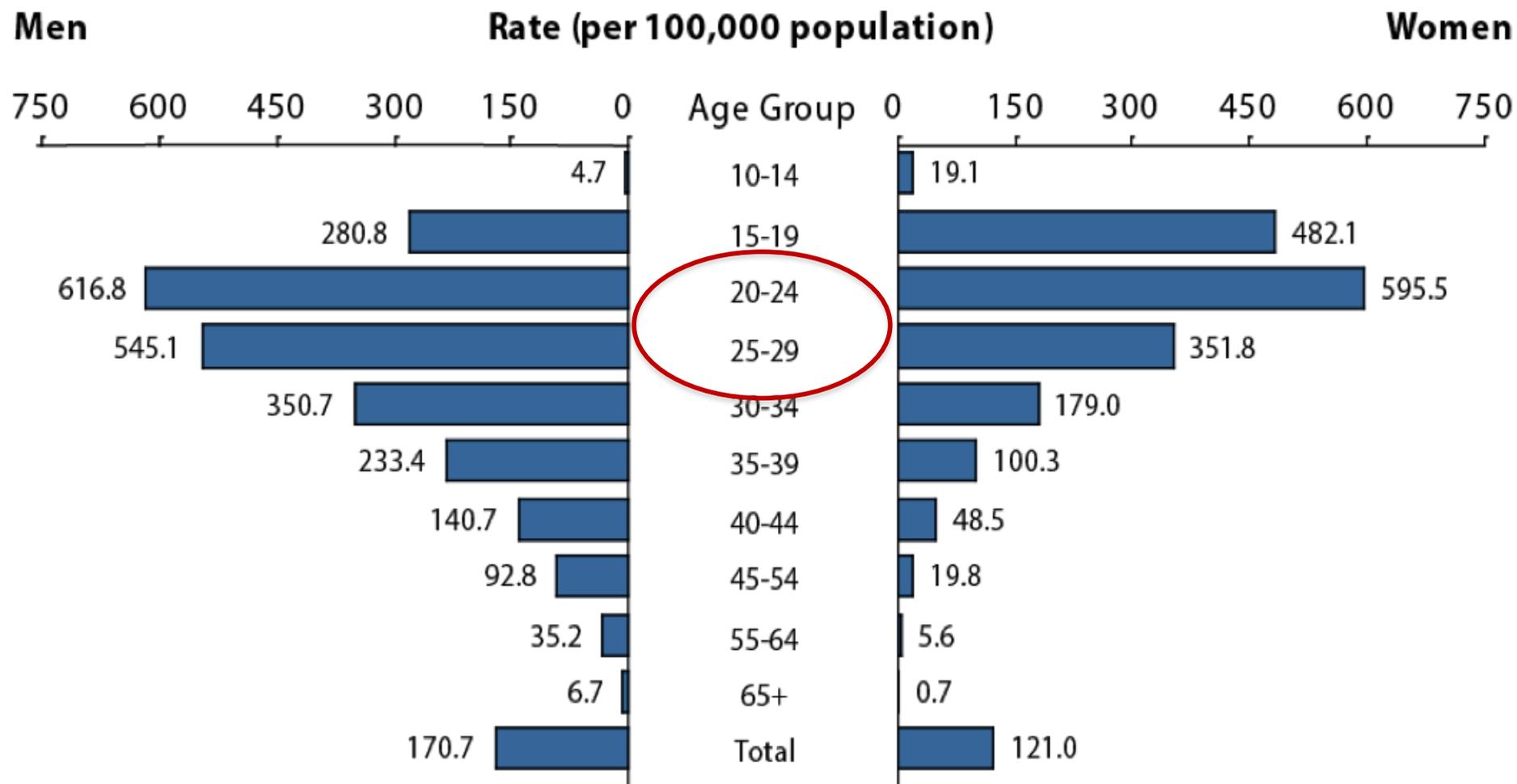
In 2016, a total of 468,514 cases of gonorrhea were reported in the US

Gonorrhea — Rates of Reported Cases by Sex, United States, 2007–2016

Rate (per 100,000 population)

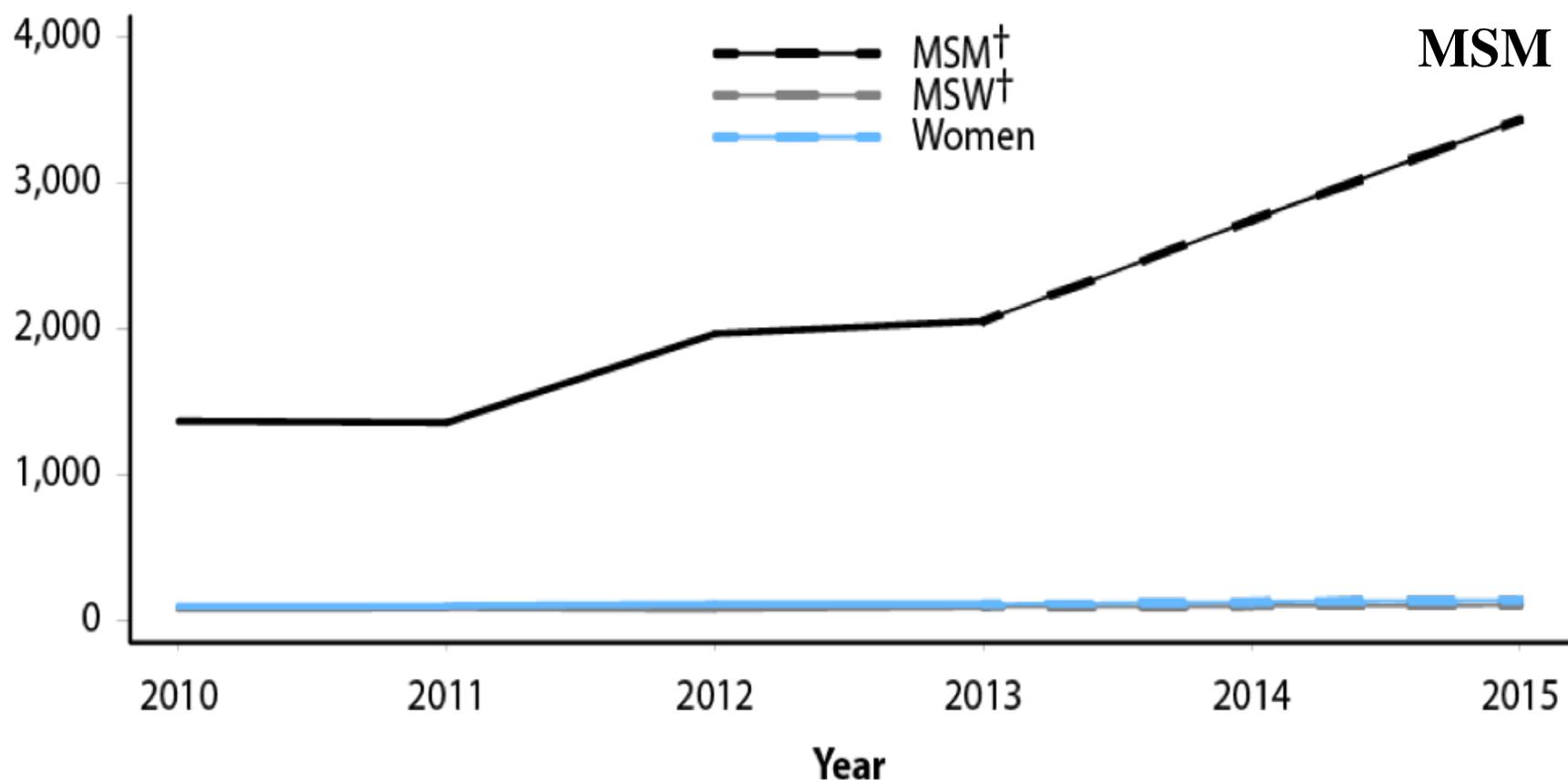


Gonorrhea — Rates of Reported Cases by Age and Sex, United States, 2016



Gonorrhea — Rates of Reported Gonorrhea by MSM[†], MSW[†], and Women, STD Surveillance Network (SSuN)[‡], 2010–2015

Rate (per 100,000 population)

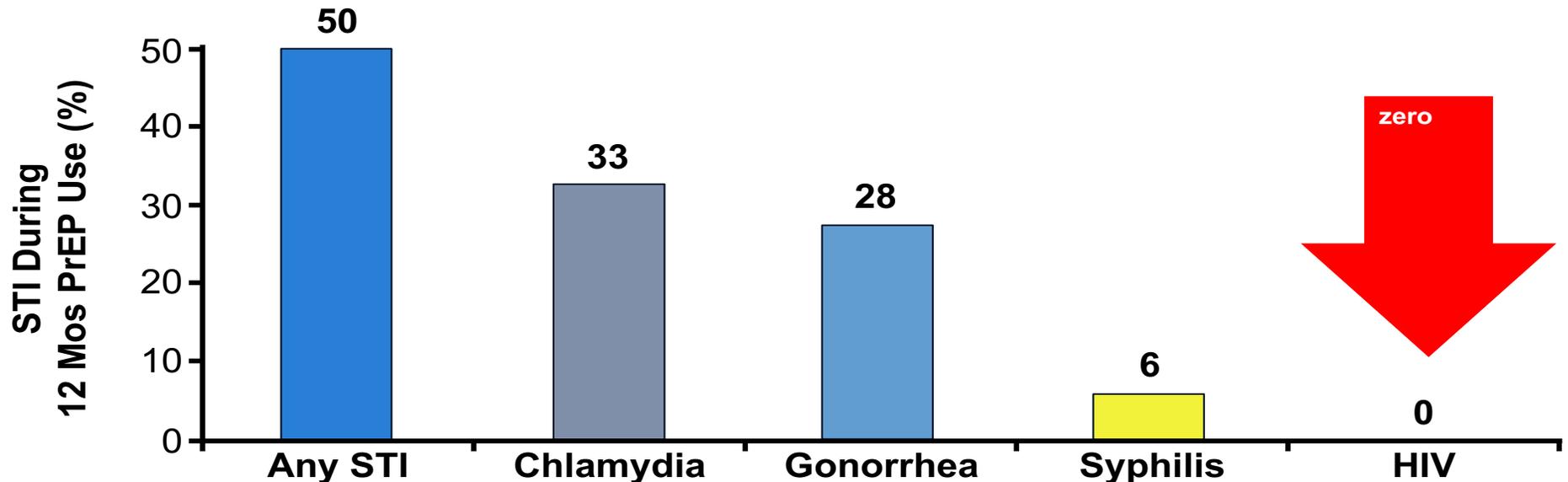


* Stenger M, Pathela P, Anschuetz G, et al. Increases in the rate of *Neisseria gonorrhoeae* among gay, bisexual and other men who have sex with men (MSM) — findings from the STD Surveillance Network 2010–2015. *Sex Transm Dis* 2017; 44(7):393–397.

STIs Will Occur for Persons Using PrEP

- Analysis of HIV/STI incidence in PrEP users in large healthcare system (Kaiser Permanente San Francisco) from 2012 to 2015

STIs in PrEP Initiators (N = 657)



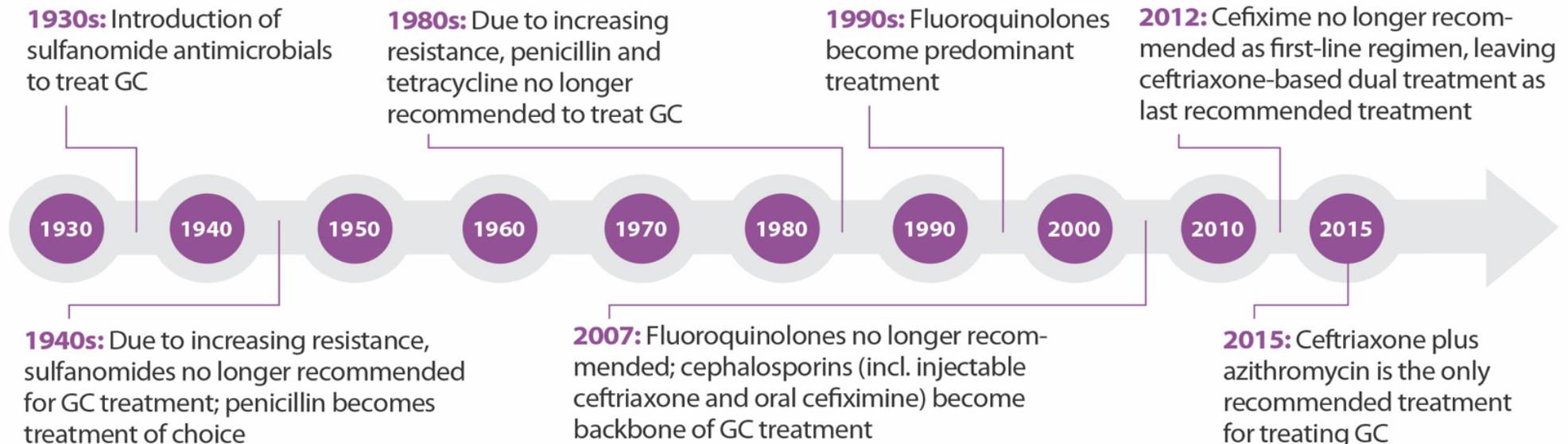
- PROUD: similar rates of any STI in 12 mos before starting PrEP (63%) vs during 12 months of PrEP (57%)^[2]

1. Volk JE, et al. Clin Infect Dis. 2015;61:1601-1603.

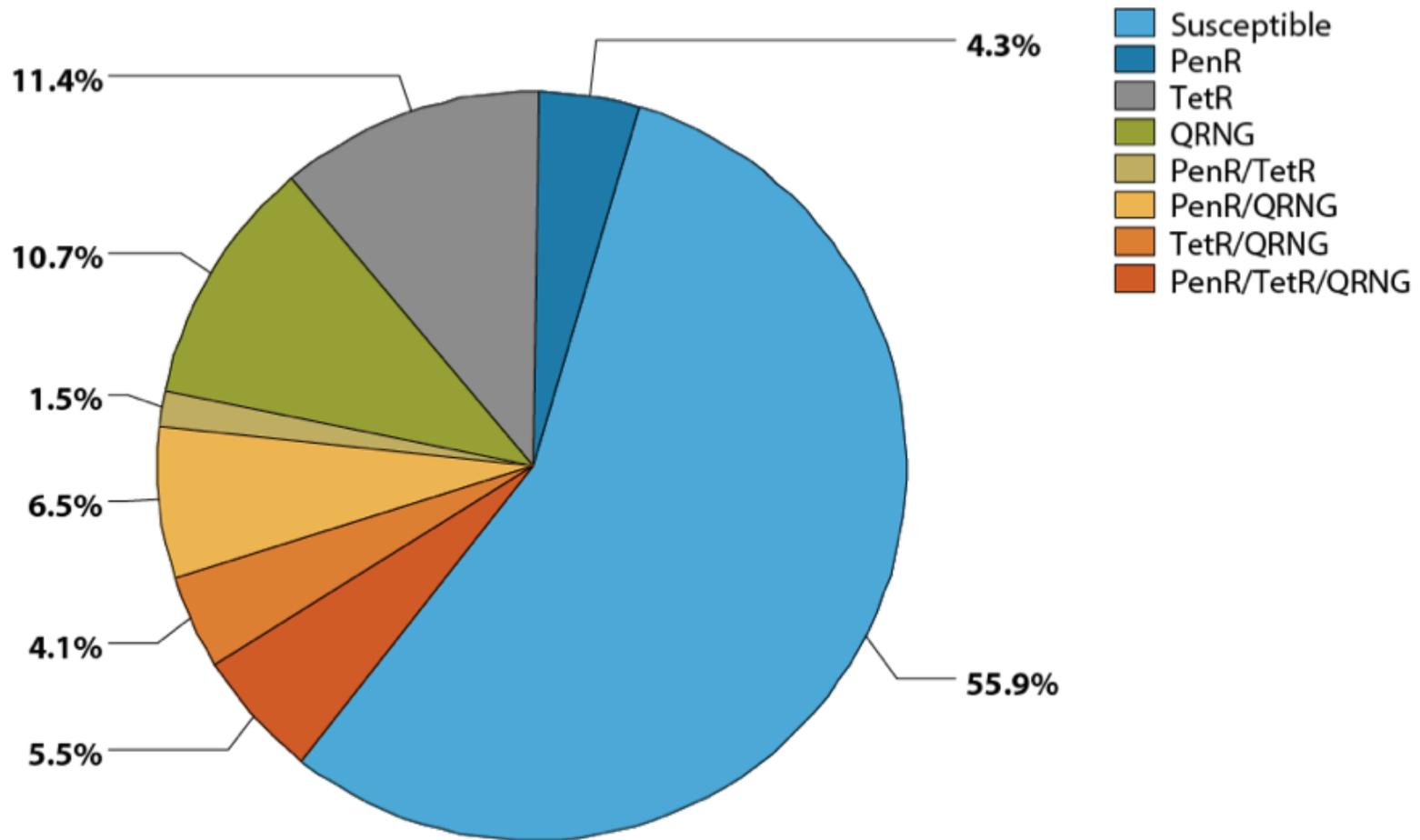
2. McCormack S, et al. Lancet. 2016;387:53-60.

Drug-Resistant Gonorrhoea

- **1940s: Sulfonamides**
- **1950s: Penicillins**
- **1960s: Tetracyclines**
- **1990s-2000s: Fluoroquinolones**
- **2010s: Azithromycin and cephalosporins**

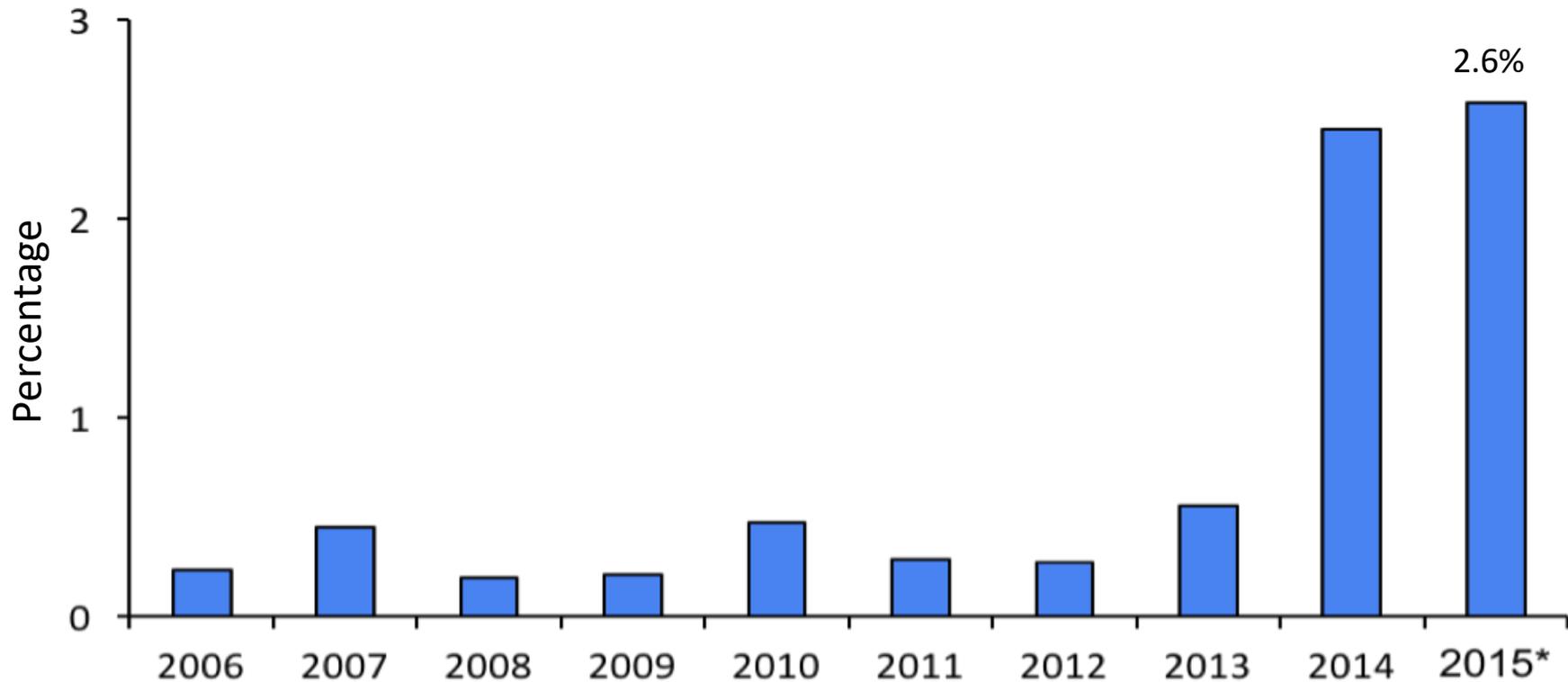


Neisseria gonorrhoeae — Distribution of Isolates with Penicillin, Tetracycline, and/or Ciprofloxacin Resistance, 2016



NOTE: PenR = penicillinase-producing *Neisseria gonorrhoeae* and chromosomally-mediated penicillin-resistant *N. gonorrhoeae*; TetR = chromosomally- and plasmid-mediated tetracycline-resistant *N. gonorrhoeae*; and QRNG = quinolone-resistant *N. gonorrhoeae*.

Percentage of GISP Isolates with Reduced Azithromycin Susceptibility (MICs ≥ 2 $\mu\text{g/ml}$) — 2006–2015*



CDC Treatment Recommendations for Gonorrhea

- **First-Line (preferred)**

- Ceftriaxone 250 mg IM X1 + Azithromycin **1g** PO X 1
- Even if *C. trachomatis* is ruled out!

- **Alternate (non-preferred):**

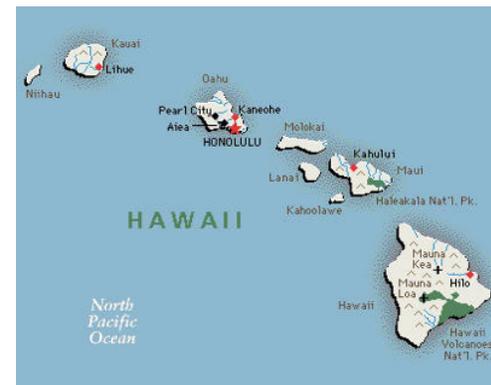
- Cefixime 400mg IM X1 + Azithromycin **1g** PO X1*

If a patient experiences cefixime treatment failure:

- Re-treat with 250 mg ceftriaxone intramuscularly and **2g** azithromycin orally
- Return for tests-of-cure within 2 weeks, preferably with culture, or, if culture is not available, with NAAT. If the follow-up NAAT result is positive, a specimen for culture should be obtained

Spreading Resistance

- **CDC press release**
 - **A cluster of GC infections in Hawaii with decreased ceftriaxone susceptibility and high level resistance to azithromycin.**



GC Drugs in Development

Drug	Class	Data
Solithromycin	Fluoroketolide	Phase II: 100% efficacy for genital, oral, and rectal; Phase III ongoing;
Zoliflodacin	Spiropyrimidinetrione topoisomerase inhibitor	Phase II showed high efficacy against urogenital infections; 98%-100% cure rate; in vitro activity against FQ-resistant and macrolide-resistant strains
Gepotidacin	Triazaacenaphthylene topoisomerase inhibitor	Phase II trial with >95% cure rates; in vitro activity against FQ-resistant and macrolide-resistant strains



AND
When the antibiotics
well runs dry....

82 Treatment of Gonorrhoea in the Male

meter. This instrument, when introduced into the urethra, can be expanded/at will, the degree of expansion being

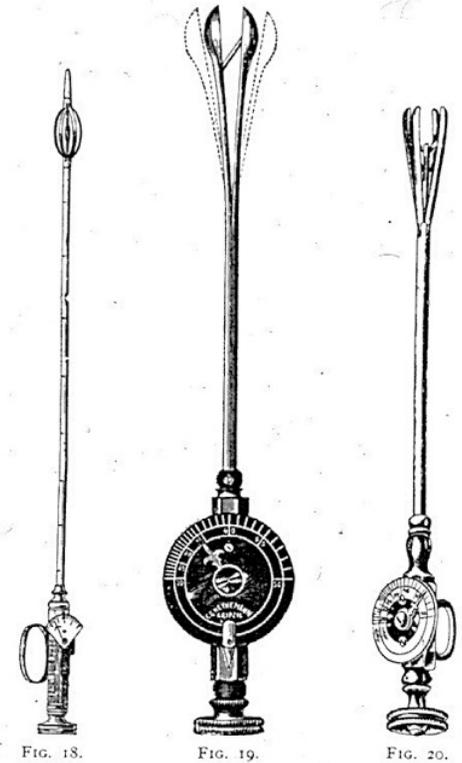
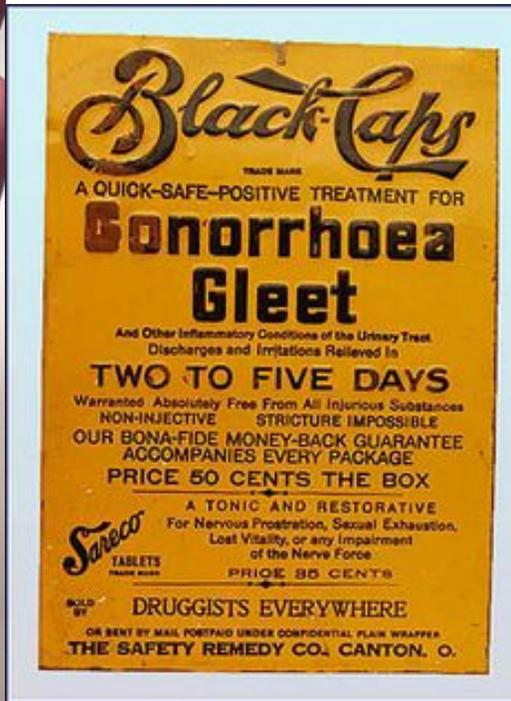


FIG. 18.

FIG. 19.

FIG. 20.

indicated by a pointer on a dial. The figures on the dial correspond to the French, or Charrière's, scale for all urethral instruments. In this scale each number represents

Patient with Eye Pain

- 58 y/o man R eye pain and redness X 4 days
 - No medical care X 20 years
 - No sex in the past 4 years
 - Right eye: Panuveitis
 - Serum CIA reactive; RPR 1:128

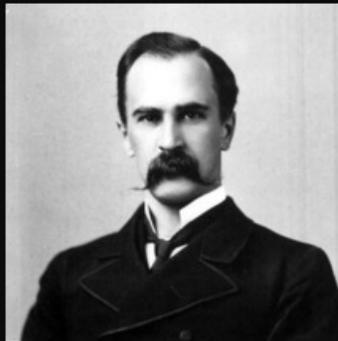
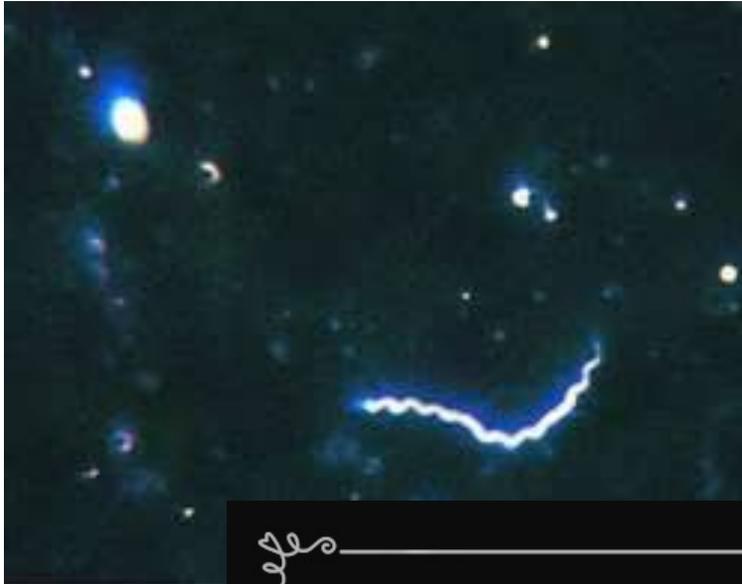


Patient with hearing loss

36 year old gay man with sudden onset of fluctuating bilateral hearing loss and tinnitus

- Sensorineural with poor word discrimination**
- Diffuse maculopapular rash on trunk sparing palms and soles**
- Serum CIA reactive; RPR 1:2048**

Treponema pallidum

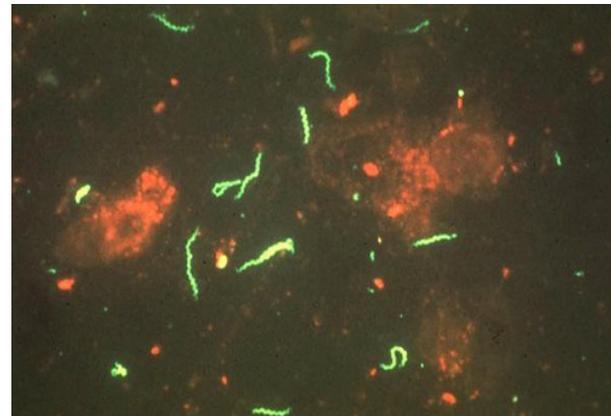


He who knows syphilis knows
medicine

~ William Osler

Syphilis

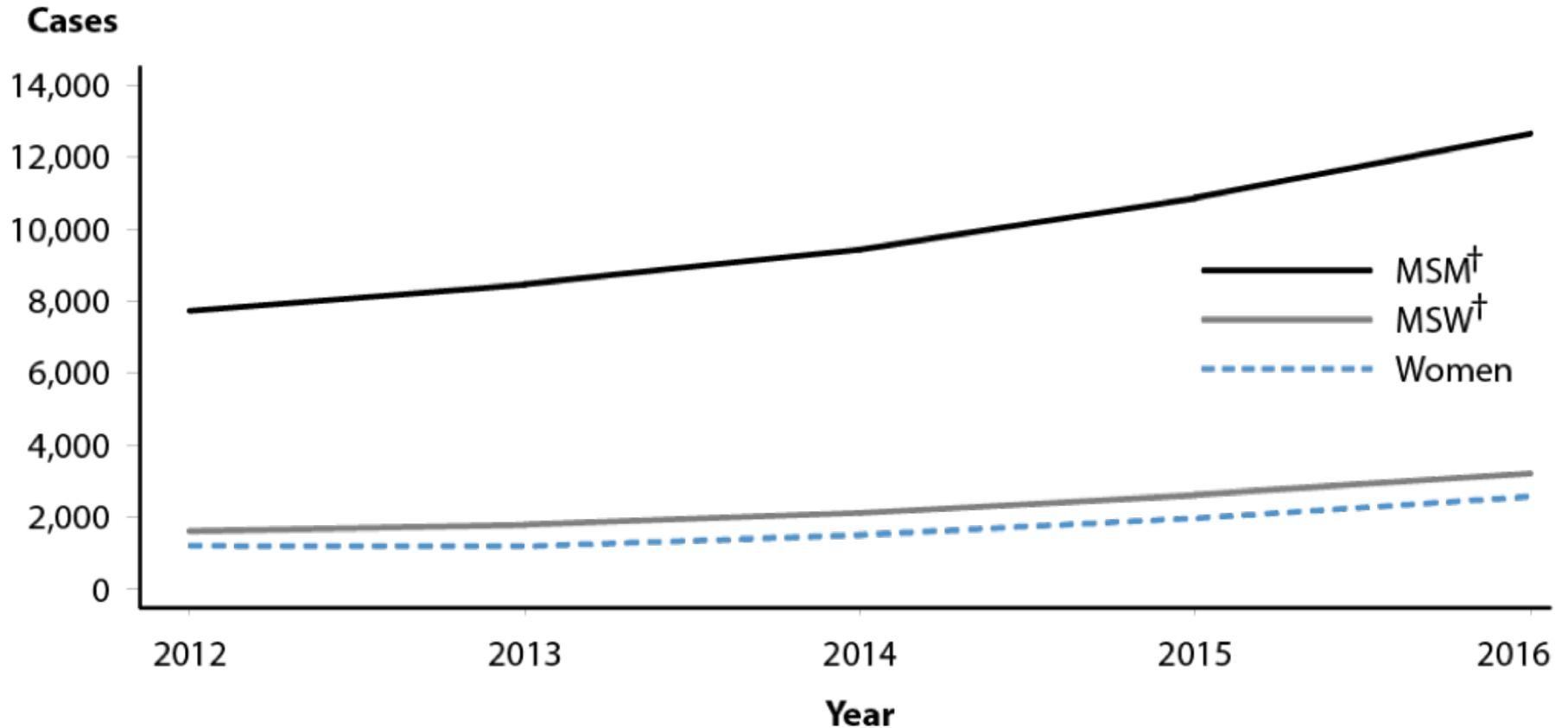
- **Primary infection (painless ulcer or chancre at the infection site- heaped-up border with clean base)**
- **Secondary infection (skin rash-palms and soles, mucocutaneous lesions, and lymphadenopathy)**
- **Tertiary infection (cardiac, gummatous, or neurological lesions)**



Secondary Syphilis



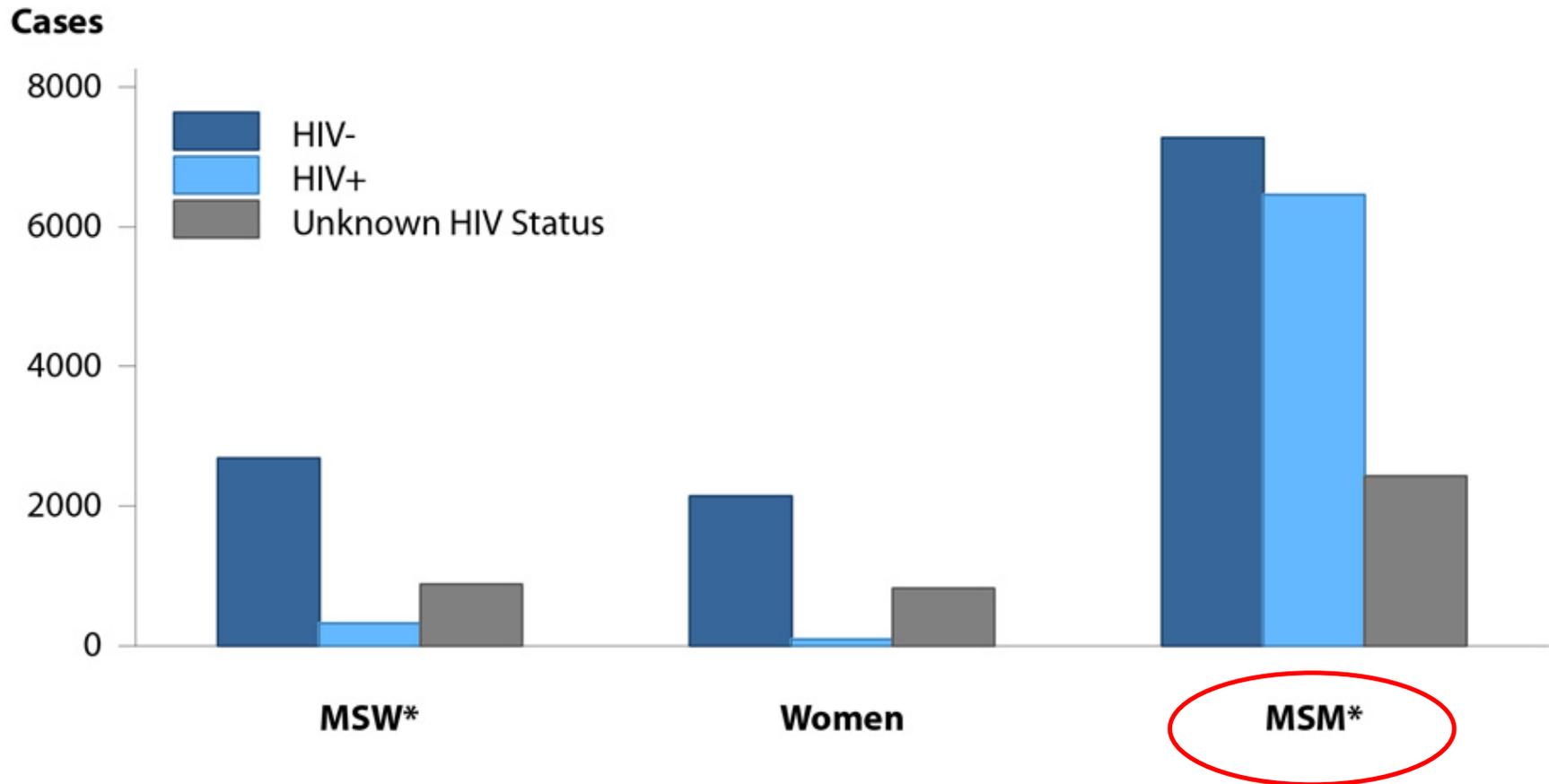
Primary and Secondary Syphilis — Reported Cases by Sex and Sexual Behavior, 36 States*, 2012–2016



* 36 states were able to classify $\geq 70\%$ of reported cases of primary and secondary syphilis as either MSM†, MSW†, or women for each year during 2012–2016.

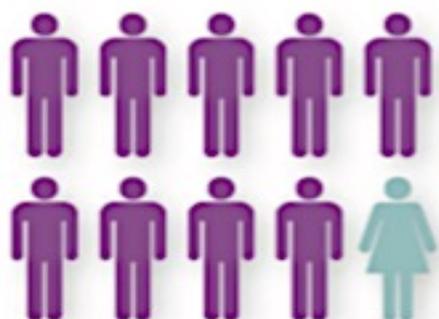
† MSM = Gay, bisexual, and other men who have sex with men (collectively referred to as MSM); MSW = Men who have sex with women only.

US Primary and Secondary Syphilis



17.6% increase 2016! 14.7% increase in men; 35.7% increase in women

STDs accelerating among men, particularly gay and bisexual men



Men accounted for more than **89 percent** (24,724) of all primary and secondary syphilis cases in 2016.



Rates increased among men by **15 percent** – from 14 cases per 100,000 men in 2015 to 16 per 100,000 men in 2016.

From 2015 to 2016, rates of syphilis increased:

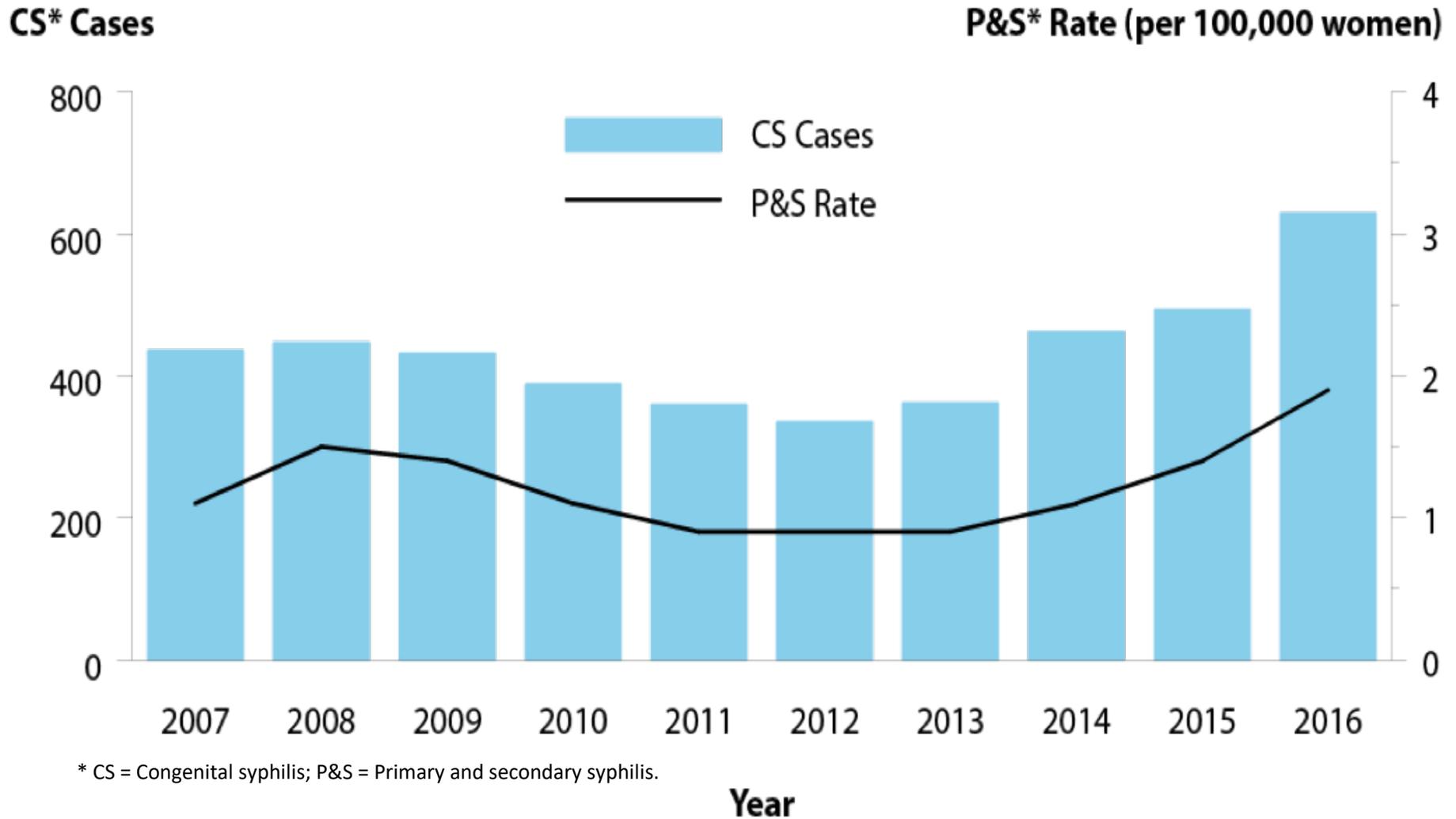
Among women

- By 36 percent
- From 1 case per 100,000 women in 2015 to 2 per 100,000 women in 2016

Among newborns (congenital syphilis)

- By 28 percent
- From 12 cases per 100,000 live births in 2015 to 16 per 100,000 live births in 2016

Congenital Syphilis — Reported Cases by Year of Birth and Rates of Reported Cases of Primary and Secondary Syphilis Among Women, U.S., 2007–2016

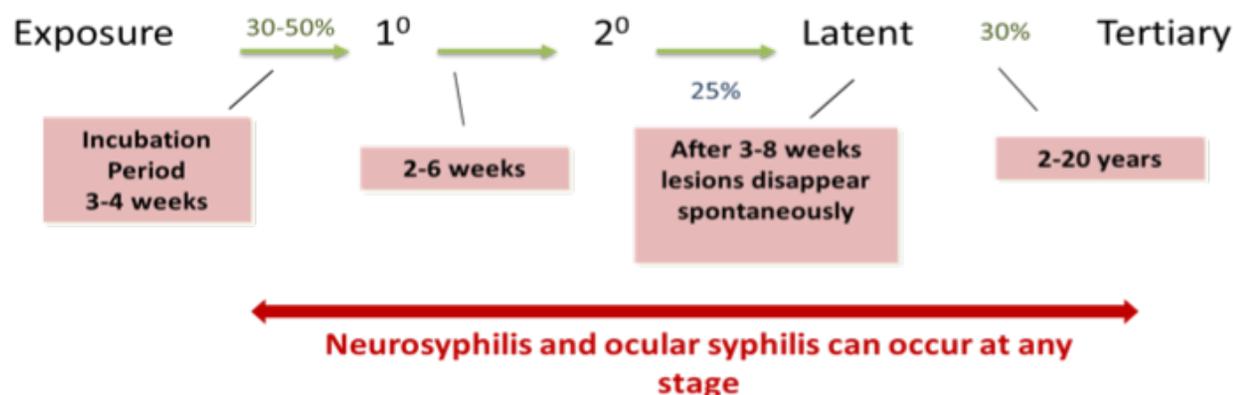


Syphilis therapy

- Early stages (primary, secondary, early latent)
 - 2.4 MU of **long-acting** benzathine penicillin or doxycycline 100mg PO BID X 14 days
- Late latent/unknown duration
 - 2.4 MU of long acting benzathine penicillin G IM X3 (over 2 weeks) [7.2 MU total] or doxycycline 100mg po BID X 4 weeks
- Neurosyphilis
 - Aqueous penicillin 18 to 24 MU IV X 10-14 days
 - Procaine penicillin 2.4 MU IM + probenecid 500 mg po QID X 10-14 days
 - Ceftriaxone 1-2g IV/IM X 10-14 days
- **Jarisch-Herxheimer:** within 6 hours after therapy of early syphilis; antipyretics only; may induce early labor

What stage(s) of syphilis involves the eye? What part(s) of the eye is/are involved?

- **Every** part of the eye can be involved during **any** stage of the infection
- Majority of eye manifestations associated with syphilis are also associated with many other infectious and non-infectious diseases.



Congenital syphilis: This group embraces notably patients with interstitial keratitis.

Secondary and late secondary syphilis: This group embraces patients with uveitis and chorioretinitis.

Tertiary syphilis: This group embraces mostly patients who present pathologic changes in the fundi, also many patients with doubtfully non-syphilitic eye lesions but with positive Wassermann reactions, and those patients with preoperative positive Wasserman reactions.

Neurosyphilis: This group notably embraces patients with optic atrophy and with ocular muscle paralysis.

Ocular Syphilis

Manifestations:

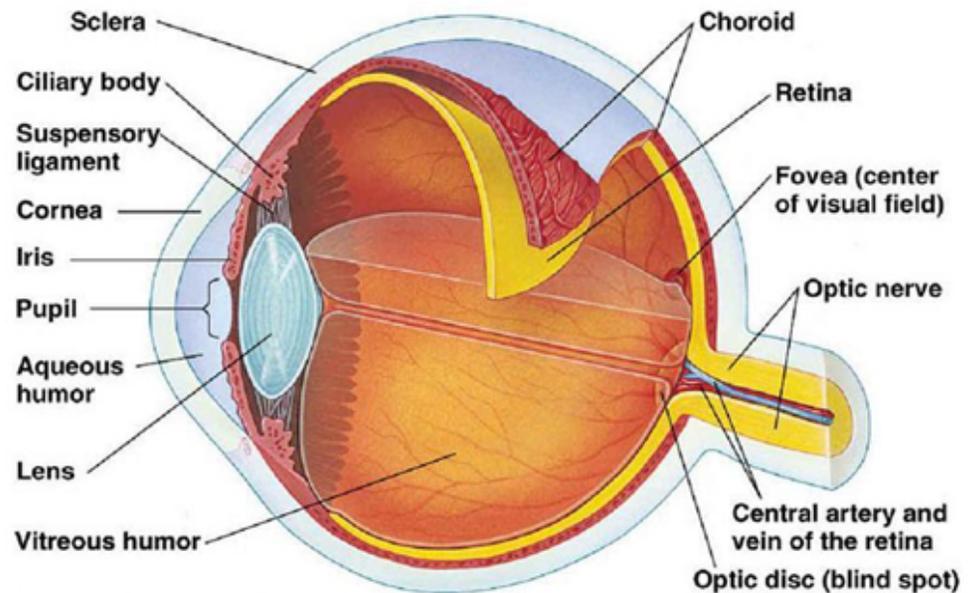
- Conjunctivitis, scleritis, and episcleritis
- **Uveitis:** anterior and/or posterior
- Elevated intraocular pressure
- **Chorioretinitis,** retinitis
- Vasculitis

Symptoms:

- Redness
- Eye pain
- Floaters
- Flashing lights
- Visual acuity loss
- Blindness

Diagnosis:

- Ophthalmologic exam
- Serologies: RPR, treponemal tests
- Lumbar puncture



**The lumbar puncture in this patient was abnormal.
What should you treat him with?**

- A. BPG 2.4 MU X 1**
- B. BPG 2.4 MU X 3 doses one week apart**
- C. Aqueous Penicillin G 24 MU per day X 10 days**
- D. Prednisone 60mg PO daily X 10 days**

Patient with hearing loss

- **IV aqueous crystalline penicillin G 4,000,000 units IV q 4 hours + steroids X 10 days**
- **JH reaction after 1st dose of penicillin**
- **Complete resolution of symptoms 1 month after therapy**

Otosyphilis

- **Diagnostic criteria:** cochleovestibular dysfunction and syphilis infection without an alternate diagnosis; ~50% bilateral
 - Diagnosis is presumptive; **CSF examination is normal in 90% of cases**
- **Therapy:** IV penicillin (+ corticosteroids)
- **Prognosis:** 23% experience improvement in hearing; up to 80% experience improvement in tinnitus and vertigo
 - Absence of hearing fluctuations, longer duration of symptoms, and age >60 years are bad prognostic indicators

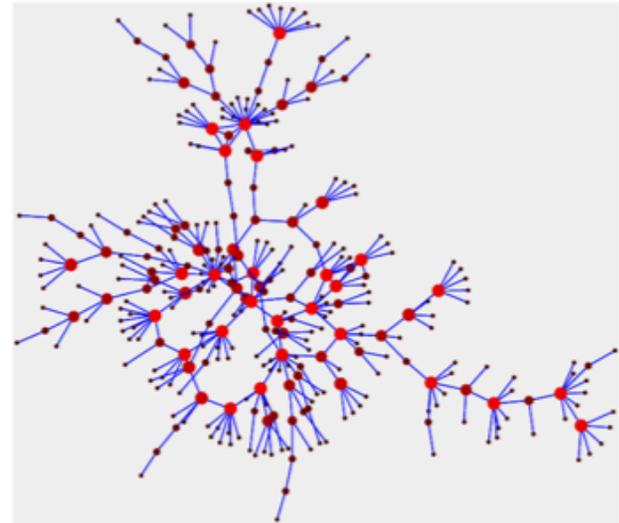
Laryngoscope 1973; 83:865-70

Laryngoscope 1977; 87:1765-1769

Laryngoscope 1992; 102:1255-9

Laryngoscope 1983; 93:154

Laryngoscope 1984; 94:753-57



STRATEGIES AND APPROACHES FOR STD PREVENTION AND CONTROL

STD Prevention and Control Strategies

- **Prevent**
 - **Health Education and Promotion**
 - **Behavioral Interventions**
 - **Vaccination (HBV and HPV)**
- **Detect and Link to Care**
 - **Screening of Asymptomatic Persons**
 - **Diagnosis of Symptomatic Persons**
- **Treatment and Follow up**
- **Case--Partner management and counseling**

Public Health Interventions to Increase Screening

- **Clinical Settings**
- **Community outreach**
 - **Mobile vans**
 - **Venue-based- pharmacies, bars, health fairs, hairs salons etc**
 - **Field-based through contact tracing programs**
- **Online internet or smart phone outreach**
 - **I Want The Kit**
 - **Internet sites offering STD testing**
 - **Order online, mail self-collected specimen, test in lab**
 - **Order online, collect and test at home, instant results**
 - **E-STD Services for STD diagnosis and treatment**
 - **E-testing and e-prescriptions**
 - **For patients and partners**

“*ASSURED*” Criteria for POC

Affordable: by those at risk of infection

Sensitive: few false negatives

Specific: few false positives

User-friendly and simple to perform: 3-4 steps, minimal training

Rapid and Robust

rapid: enable treatment at first visit

robust: no refrigerated storage

Equipment-free: easily collected non-invasive specimens

Delivered: delivered to end-users

RDTs for *Trichomonas vaginalis*

XenoStrip-TV (Xenotop
Diagnostics, San Francisco,
CA, USA)
OSOM Trichomonas Test
(Sekisui Diagnostics,
Lexington, MA, USA)



**For *T vaginalis* and
HPV**
GeneXpert (Cepheid,
Sunnyvale, CA, USA)



**For *C trachomatis*,
duplex *C trachomatis*
and *N gonorrhoeae*,
and *T vaginalis***
io System (Atlas
Genetics, Trowbridge, UK)



**For *C trachomatis* and
*N gonorrhoeae***
Alere i (Alere, Waltham,
MA, USA)



STI assays under consideration
Cobas Liat Analyzer
(Roche, Basel,
Switzerland)



**Specific STI assays
unknown**
PanNAT (Micronics,
Portsmouth, NH, USA)



Before
2014

2014

2015

2016

2017-18



**For *Chlamydia trachomatis*,
Neisseria gonorrhoeae,
and duplex *C trachomatis*
and *N gonorrhoeae***
GeneXpert (Cepheid)



For *T vaginalis*
AmpliVue (Quidel,
San Diego, CA, USA)



**For *C trachomatis* and
*N gonorrhoeae***
Truelab™ Real Time
quantitative micro
PCR system (Molbio
Diagnostics, Goa,
India)



**For duplex *C trachomatis*
and *N gonorrhoeae*,
and HPV**
GeneXpert Omni
(Cepheid)



For *C trachomatis*
RT Cross-Priming
Amplification
CT Test (Ustar
Biotechnologies,
Hangzhou, China)

SD BIOLINE
HIV/Syphilis Duo
Rapid Test (Aleris,
Waltham, MA, USA;
Standard Diagnostics,
Yongin, South Korea)



DPP HIV-Syphilis
Assay (Chembio
Diagnostic Systems,
Medford, MA, USA)



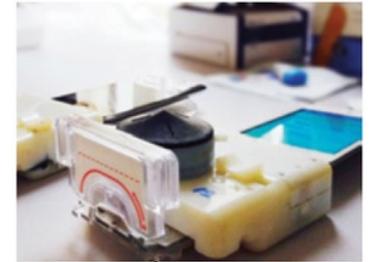
Multiplo Rapid
TP/HIV Antibody
Test (MedMira, Halifax,
Canada)



INSTI HIV/Syphilis
Multiplex Test
(bioLytical Laboratories,
Richmond, Canada)



mChip Assay (Junco
Labs, Columbia
University, New York,
NY, USA; in
collaboration with
OPKO Health, Miami,
FL, USA)



2013

2014

2015

2017

Disposable

Device

Acknowledgements

- **Many thanks to the following for slides and discussions.**
 - **Charlotte Gaydos, DrPH**
 - **Jonathan Zenilman, MD**
 - **Anne Rompalo, MD, MPH**
 - **Khalil Ghanem, MD, PhD**